Congenital Diaphragmatic Hernia and Extracorporeal Membrane Oxygenation

Frans van der Staak

Congenital Diaphragmatic Hernia

and

Extracorporeal Membrane Oxygenation

Congenital Diaphragmatic Hernia and Extracorporeal Membrane Oxygenation

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Abbreviations

$AaDO_2$	=	alveolar to arterial oxygen pressure gradient (difference)
ACT	=	activated clotting time
BAER	=	brainstem auditory evoked response
$BPDPO_2$	=	best postductal paO_2
CDH	=	congenital diaphragmatic hernia
CHD	=	congenitale hernia diaphragmatica
CLD	=	chronic lung disease
CPB	=	cardiopulmonary bypass
CRAD	=	chronic reactive airway disease
CT	=	conventional treatment
CT-scan	=	computer tomography
DIC	=	disseminated intravasal coagulopathy
DQ	=	developmental quotient
EACA	=	epsilon aminocaproic acid
ECC	=	extracorporeal circulation
ECLS	=	extracorporeal life support
ECMO	=	extracorporeal membrane oxygenation
ELSO	=	extracorporeal life support organization
FiO_2	=	fraction of inspired oxygen
GER	=	gastroesophageal reflux
HFJV	=	high frequency jet ventilation
HFOV	=	high frequency oscillatory ventilation
HFPPV	=	high frequency positive pressure ventilation
HR	=	high risk
HUS	=	head ultrasonography
ICH	=	intracranial hemorrhage
ITPV	=	intratracheal pulmonary ventilation
kPa	=	kiloPascal (1 kPa ~ 7,5 mm Hg)
LES	=	lower esophageal sphincter
MQ	=	motor quotient
MAP	=	mean airway pressure
MAS	=	meconium aspiration syndrome
MCT	=	medium chain triglycerides
MDI	=	mental developmental index
mm Hg	=	millimeters mercury (pressure)
NO	=	nitric oxide
NT	=	not traceable

OI	=	oxygenation index (MAP x FiO_2 x 100/PaO_2)
OR	=	oddsratio
P10, P25	=	percentile (10th,25th respectively)
$PaCO_2$	=	arterial partial carbondioxide pressure
$PACO_2$	=	alveolar partial carbondioxide pressure
PAI	=	plasminogen activator inhibitor
PaO_2	=	arterial partial oxygen pressure
PAO_2	=	alveolar partial oxygen pressure
PAP	=	pulmonary arterial pressure
Pbaro	=	atmospheric pressure
PDA	=	persistent ductus arteriosus
PEEP	=	positive end exspiratory pressure
PFC	=	persistent fetal circulation
pH	=	negative logarithm of free hydrogen ion concentration
pH_2O	=	partial vapour pressure (47 mm Hg at 37°C)
PIE	=	pulmonary insterstitial emphysema
PIP	=	peak inspiratory pressure
PLV	=	partial liquid ventilation
PPHN	=	persistent pulmonary hypertension of the newborn
PTFE	=	polytetrafluoroethylene (Goretex ^{R})
PVR	=	pulmonary vascular resistance
RBC	=	red blood cells
RDS	=	respiratory distress syndrome
SaO_2	=	arterial oxygen saturation
SCV	=	superior caval vein
SD	=	standard deviation
TEA	=	tranexamic acid
TPA	=	tissue plasminogen activator
TRH	=	thyrotropine releasing hormone
UK	=	United Kingdom
V/Q-ratio	=	ventilation/perfusion ratio
VA-ECMO	=	venoarterial ECMO
VI	=	ventilation index (= ventilatory rate x MAP)
VV-ECMO	=	venovenous ECMO
X-ray	=	radiographic examinations

Prologue

A congenital diaphragmatic hernia (CDH) concerns a developmental anomaly, in which there is an incomplete formation of the diaphragm. Generally, this anomaly is classified into 2 categories according to the location of the defect
1 the ventral or retrosternal defect, usually designated as a hernia of Morgagni and
2 the posterolateral defect, usually designated as a hernia of Bochdalek.
Although Bochdalek originally described a herniation through the trigonum lumbocostale his name is erroneously attached to all forms of posterolateral defects. This thesis is exclusively dealing with the congenital posterolateral defect, which constitutes a serious malformation that may cause severe respiratory distress and death immediately after birth.

Despite improvements in perinatal and neonatal care, in artificial ventilation and in neonatal transportation the mortality rate for this anomaly has been remained continuously high in the past 3 or 4 decades -amounting to 50 to 60% in high risk infants. Those infants have symptoms of respiratory distress within 6 hours after birth In view of these disappointing results alternative modes of therapy were explored, among which extracorporeal membrane oxygenation (ECMO).

ECMO is a technique in which the blood circulates outside the body (extracorporeal) and in which the gas exchange of the blood occurs across a semipermeable membrane of an "artificial lung" (the membrane oxygenator). Since the blood is constantly in contact with the foreign surface of the extracorporeal circuit there is an increased risk of clot formation. Thus in order to prevent those clots anticoagulation therapy is required. However, that therapy ensues risk of bleeding complications. Not only for these risks as well as for the aggressive (invasive) nature of this technique, ECMO treatment is considered as a therapy of last resort. It is only applied in infants who are unresponsive to other extreme measures (maximal conventional therapy) and who would very likely die.

However problems for such last-resort therapy are how to identify those patients who have no likelihood of survival using other less invasive and less risky therapies and at which point in the course of the illness the last-resort therapy has to be implemented. Because ECMO is used only in patients who are most likely to die otherwise, the results are usually described in terms of simple survival. Nevertheless long-term quality of life is also important.

This thesis presents clinical studies of congenital diaphragmatic hernia in relation to the use of extracorporeal membrane oxygenation The core of this thesis is formed by published papers concerning outcome prediction and patient selection for ECMO, the early experience and the improving survival with ECMO and complications encountered in the treatment of congenital diaphragmatic hernia, and a submitted paper regarding the early morbidity and outcome of ECMO CDH survivors. These papers are preceded by introductory chapters on congenital diaphragmatic hernia and on extracorporeal membrane oxygenation.

Part I Introduction

Chapter 1

Congenital Diaphragmatic Hernia

1.1 Introduction

1.2 Pathophysiologic considerations

1.2.1 Historical concept: mechanical compression

1.2.2 Pulmonary hypoplasia

1.2.3 Pulmonary hypertension

1.2.4 Transthoracic Pressure Gradient

1.3 Treatment strategies and therapeutic aspects

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1.3.2 Delayed surgery

1.3.3 Miscellaneous Management Aspects

1.4 Assessment of severity of disease and prediction of outcome in CDH

1.1 Introduction

Congenital Diaphragmatic Hernia entails a developmental defect in which the usual closing process of the diaphragm has been arrested or disturbed before birth. An incompletely closed diaphragm results in a free communication between the pleural and peritoneal cavity and allows abdominal viscera to move into the thorax. Various parts of the diaphragm can be affected. Generally congenital diaphragmatic hernias are divided into 2 categories according to the location of the defect:

a. in the retrosternal area: the foramen of Morgagni
b. in either posterolateral portion, along the old pleuroperitoneal canal: the foramen of Bochdalek.

The posterolateral hernia is the most common diaphragmatic defect – it comprises 85% of all congenital diaphragmatic hernias[1] – and remains a critical problem in neonatal surgery, since it is associated with a high mortality[2-9].
The congenital posterolateral diaphragmatic hernia is a distinct entity and constitutes the subject of this discussion. In the following text congenital diaphragmatic hernia (CDH) without further indication means a posterolateral hernia.

The cause of the closing defect of the diaphragm is still unknown[10-12].
The reported incidence of CDH varies from 1 in 2400 to 1 in 5000 liveborns[2,4,13,14]. CDH may be accompanied by other malformations in about 50% of the cases[1,4,15-17]. Most common associated malformations are neural tube defects and cardiac defects, especially in stillborns[1,4,15,18-20]. Diaphragmatic defects have been reported in association with chromosomal defects (most commonly trisomies 18 and 21)[19], as part of a syndrome[15,20-23] and as a familial occurence[24-27]. Left sided defects occur more frequently than right sided defects (80% to 20%)[16].

Serious clinical symptoms of respiratory distress may occur in CDH-patients shortly after birth. The respiratory insufficiency is responsible for a mortality rate of 40% to 60%[2,3].
Despite a succesful repair of the defect and despite all advances and enormous efforts in neonatal care, including prenatal diagnosis, neonatal transport, intensive care treatment and anaesthesiology, this mortality rate seems to increase rather than to drop[2,3,28,29].
Gross' suggestion, that babies and children with diaphragmatic hernias can be cured of their malformation in 90% to 95% of the cases by surgical repair, did not come true[30].
The management of CDH-patients turned out to be more complex than the simple surgical

closure of the diaphragmatic defect and the withdrawal of abdominal viscera from the thoracic cavity The pathophysiology of this anomaly appeared to be more complex

1.2 Pathophysiologic considerations

1.2.1 Historical Concept mechnical compression

In the early days of paediatric surgery it was thought that the pathologic condition in CDH patients was a pure mechnical problem[31 32]. Since there is no complete separation between the thoracic and abdominal cavity the pleural cavity is filled with abdominal viscera Postnatally the protruded intestines fill with air after the first breath and exert pressure upon the lungs and mediastinum. The lung on the affected side may be completely collapsed, the heart has been pushed to the opposite side of the chest and the contralateral lung is generally partially compressed.

"The severity of symptoms and the speed with which they appear depend on the extent to which the abdominal viscera are drawn into the chest and on the degree to which the lungs are compressed" (Gross 1946). Hence Gross stated, that "surgical intervention should be employed as soon as the diagnosis is made"[31]

The abdominal viscera should be pulled down out of the chest in order to alleviate the respiratory embarassment. In those days rapid expansion of the collapsed lung seemed to be highly desirable as well as "to suck the air out of the pleural cavity, which allows the mediastinum to return to a normal position and gives maximum aeration of the lungs"[31]. However emergency surgery did not provide the success that was expected, since there was another pathologic phenomenon· pulmonary hypoplasia.

1 2.2 Pulmonary hypoplasia

Pulmonary hypoplasia as the underlying secundary pathophysiological abnormality in congenital diaphragmatic hernia was described by Campanale and Rowland[33]

It was supposed that the prenatal compression of the protuded abdominal viscera on the lung buds causes hypoplasia of the developing lungs. Experimentally it was shown that artificially induced pressure on developing lung tissue may cause hypoplasia[34]. The severity of the hypoplasia should depend on the stage of development which the lungs had achieved at the time of the experiment [34 35]. Although the term hypoplasia is not well defined it is obvious that lung development in babies with diaphragmatic hernia is abnormal[36].

Several studies have been performed to describe and to quantify the "degree" of pulmonary

hypoplasia [34 35 37 43]. It has been shown that not only the lung weight in reference to the body weight is reduced in CDH-patients [1 37 39], but also that each of the functional systems within the lung is affected [40 42]. Areechon and Reid found a reduced number of conducting airways – especially on the affected side – and concluded that the bronchial branching was arrested [42]. In connection with the reduction of the number of airway generations a reduction in the volume and number of alveoli was found as well [38 39 42]

In addition to the reduced respiratory exchange surfaces the air-blood interface is thickened in comparison to normal lungs [41]. It was demonstrated in animal studies that although type II pneumocytes – which are considered to be responsible for the production of surfactant – are increased in the lungs of lambs with CDH, the type II cells are immature with less lamellar bodies which are responsible for the storage of surfactant [44 45] Besides these structural parenchymal abnormalities, functional parenchymal abnormalities are present as well. Not only may the surfactant production be impaired, but the composition of surfactant may be aberrant as well as having a decreased phosphatidylcholine content [41 46]. Both conditions can result in a less efficacious surfactant system in CDH. On the other hand animal studies have suggested that the antioxidant defense system may be impaired in neonates with CDH [47 48]. Last but not least vascular development has been involved in the pulmonary hypoplasia of congenital diaphragmatic hernia [40 49 51]. The numbers of conventional and supernumerary arterial branches are reduced in lungs of CDH patients, whereas there is a markedly increased muscle mass within the media. These abnormalities – underdevelopment of the pulmonary vascular bed and maldevelopment with excessive muscularisation – lay the morphological foundation of another important pathophysiological phenomenon pulmonary hypertension [52].

1.2.3 Pulmonary Hypertension

According to the aforementioned morphological findings (see 1.2.2) it was generally assumed that the high mortality in diaphragmatic hernia patients was due to pulmonary hypoplasia. However, the clinical course, frequently seen in CDH patients following repair of the diaphragmatic defect argues against the "pulmonary hypoplasia theory" as the cause of respiratory insufficiency and death.

Many infants show an adequate oxygenation in the immediate postoperative period, lasting for up to 24 to 36 hours, followed by deterioration and subsequently death [53 55].

This period of adequate oxygenation after surgical repair was described by Collins et al as the "honeymoon period" [53]. They believed that "a dynamic pathophysiologic event must account for the terminal anoxemia rather than an absolute deficiency of lung parenchyma".

It was hypothesized that the clinical deterioration could be attributed to a rise in the pulmona-

ry vascular resistance, resulting in a state of fetal circulation with right-to-left shunting through the ductus arterious, foramen ovale and intrapulmonary vessels [53 55]. Cardiac catheterization and angiography confirmed the presence of these phenomena [56,57]. This condition had been described in other neonates without CDH previously and termed persistent pulmonary hypertension of the newborn (PPHN) or "PFC" syndrome (persistent fetal circulation) [58 59]. Besides a maldevelopment and an underdevelopment (see 1.2.2) a maladaptation of the pulmonary vascular bed may be responsible for a severe pulmonary hypertension in CDH-patients [52]. An exaggerated response of the anatomically abnormal pulmonary vascular bed can occur as a result of numerous factors among which hypoxia, acidosis and can initiate a condition of progressive hypoxemia which is responsible for the high mortality among CDH-infants.

1.2.4 Transthoracic Pressure Gradient

The hypothesis that overexpansion of the lungs might be a major cause of progressive pulmonary insufficiency led to several studies concerning the pathophysiologic consequences of transthoracic and transpleural pressure gradients on pulmonary function [60-63].
It was demonstrated in animal experiments in which the postoperative state of infants with CDH was mimicked that overdistention and a mediastinal shift resulted in a progressive respiratory insufficiency with an immediate decrease in PaO_2 and increase in $PaCO_2$ [60,63].
Cloutier supposed that the postoperative reversion to fetal circulation was due to the rapid expansion of both hypoplastic lungs. In his opinion this complication was preventable [62]. In an experimental study in lambs it was demonstrated that there is a positive correlation between the transpulmonary pressure gradient employed and the pulmonary interstitial emphysema (PIE) found at morphometry [64].
Considering these results he suggested that using low ventilatory pressures and not draining the pleural cavity resulted in less barotrauma to the lungs and might prevent one of the components of the pulmonary hypertension.

1.3 Treatment strategies and therapeutic aspects

Through the years management strategies for CDH have been determined by what was known or what was conceived with respect to the pathophysiology.

1.3.1 Emergency Surgery

Surgical repair of the diaphragmatic defect with removal of intestines from the thoracic cavity seemed the straight forward solution [30-32]. Supposing that the respiratory problems were caused by compression of the ipsilateral lung, relief of the compression should allow the lung to expand and should improve respiration. The principal drawback hampering a successful outcome was thought to be the need for major surgery in infants arriving in an already critical condition Having knowledge of lung hypoplasia and being aware of the presence of prenatal developmental factors as major determinants of outcome, the belief that CDH was a surgical emergency remained. The approach to the problem was more or less pragmatic.
After elimination of lung compression as a source of respiratory embarrassment, the most optimal condition for a good and unhampered respiration was created.
When sufficient lung tissue was present, the infant survived. But when the lung compression was relieved and the infant died, the amount of lung tissue was considered to be unable to support extrauterine life.
However, with that approach a third category of patients could be identified· the "honeymooners", in whom abnormalities of the pulmonary vascular bed and right-to-left shunting determined the clinical picture and the clinical course [53]. According to Pringle [36] there appear to be 3 clearly defined groups.

1. Those patients who present with few or no respiratory symptoms. They almost all survive.
2. Those patients that can never be adequately oxygenated and die shortly after birth, regardless of the kind of treament
3. Those infants that initially appear to do well or respond very well to intubation and ventilation but who later develop PPHN. This group has a rather poor survival.

Urgent, probably lifesaving, surgical repair continued but therapeutic efforts were concentrated on the management of PPHN [53 65].
Treatment protocols included hyperventilation, alkalinization and muscle paralysis whereas several vasoactive drugs were tried in an attempt to manipulate the pulmonary circulation [53 65 67]. In individual cases a temporary (and sometimes a definite) reversion of the pulmonary hypertension could be achieved, but survival on the whole did not improve.

1.3 2 Delayed Surgery

Up to the 1980s emergency surgical repair was the cornerstone of the therapeutical approach. Changing insights in the pathophysiology of CDH brought about a major revolution in the treatment of CDH with a strategy of delayed surgery after a period of preoperative stabilizati-

on [5 9] (table 1). This approach was prompted by studies demonstrating adverse effects on thoracic compliance and gas exchange following surgical repair of CDH [68 69]. Although delayed surgery has become the widely accepted approach to CDH-management, it is unclear whether this strategy has significant impact on survival [5 9].

Table 1 **Conventional Preoperative Stabilization**

–	nasotracheal intubation
–	mechanical positive pressure ventilation with hyperventilation and with oxygen up to 100%, if necessary
–	muscle relaxation with pancuronium
–	sedation with midazolam and/or fentanyl
–	gastrointestinal decompression by nasogastric tube
–	manipulation of the systemic circulation with vasoactive drugs (dopamine, dobutamine or isoprenaline)
–	manipulation of pulmonary circulation (tolazoline)

It was assumed that the surgical stress and the mechanical effects of hernia repair elicit or aggravate pulmonary hypertension and right-to-left shunting. It seemed better to avoid a surgical procedure until the unstable pulmonary circulation became less reactive However, clear criteria for how long operation should be deferred are lacking, it is more or less a matter of clinical judgment and prolonged experience [6 7].

Using echocardiographic monitoring of pulmonary arterial pressure (PAP) Haugen et al recommend postponement of the operation until pulmonary vascular resistance (PVR) has decreased [70]. Reduction of PVR was presumed when PAP had fallen to a level of 25 to 55 mmHg and a bidirectional or right-to-left shunt through the ductus arteriosus was reversed to a left-to-right shunt By continuous measurements of physiological variables Moffitt et al have attempted – as part of their study – to identify the achievement of medical stabilization [71]. There is conflicting evidence whether delayed surgery results in an improvement in survival compared to emergency surgery In only 2 series of CDH-patients treated with delayed surgery has a reduced mortality been reported [5 6] All other series have not noted a major difference in survival [8 9 72]. Two randomized controlled trials did not show any difference in survival between delayed versus immediate repair either [73 74]

1.3.3 Miscellaneous Management Aspects

Being aware of the presence of lung hypoplasia in all its gradations, several refinements in the therapeutic management of CDH have been advocated.

Since hypoplastic lungs are susceptible to barotrauma special surgical approaches have been proposed to avoid overexpansion of the hypoplastic lung. In order to control excessive intrathoracic pressure gradients "balanced" thoracic drainage and mediastinal stabilization by an expansion prosthesis are employed [75, 76]. For the same purpose a chest tube attached to an underwater seal is recommended postoperatively instead of chest drainage with suction [62]. Reconstruction of the dome of the diaphragm with the use of a prosthetic patch should be pursued in every diaphragmatic defect [77].

Hyperventilation as the mainstay treatment for all causes of PPHN including CDH has been abandoned because of hearing loss and the associated barotrauma resulting from aggressive ventilatory management. A pressure-limited ventilation ignoring hypercapnia has been advocated ("permissive hypercapnia ventilation") [78, 79].

Other ventilatory techniques without high airway pressures are currently used to avoid barotrauma: high-frequency oscillation ventilation (HFOV) [80-84] high-frequency jet ventilation (HFJV) [85] and intratracheal pulmonary ventilation (ITPV) [86]. Experience with ITPV in newborns is very limited [87]. In HFOV and HFJV improvement of gas exchange has been achieved by increasing ventilator rates (to the range of 100 to 600 breaths per minute) rather than by increasing airway pressures. The greatest experience has been accumulated with HFOV, but the place of HFOV in CDH-treatment has yet to be elucidated: neither in the hierarchy of CDH-treatment nor in terms of efficacy and contribution to improved survival [80-84].

A relative surfactant deficiency as component of the lung hypoplasia has been documented in human studies as well as in animal studies [46, 88]. Correction of this deficiency could be achieved by two alternative ways: by surfactant replacement therapy or by the prenatal administration of steroid therapy with or without thyrotropin releasing hormone (TRH) [89-92,134-136].

Application of surfactant replacement therapy in newborn infants could have a beneficial effect but the success is not unequivocal[93-95]. Prophylactic surfactant therapy is probably more efficacious than the administration of surfactant as a rescue therapy [89].

The use of liquid instead of gas as a ventilation medium in respiratory failure is still in its infancy. Preliminary clinical studies showed improvement in oxygenation and compliance in neonates with RDS as well as with CDH [96-99]. The usefulness of liquid ventilation therapy in CDH is waiting for further evaluation.

Intensive research into vasoactive mediators, which play a role in pulmonary hypertension of the newborn or which can cause selective pulmonary vasodilatation are in progress. The roles

of thromboxanes, prostaglandine and leukotrienes have been investigated [100 103] The results of prostacyclin administration in the clinical situation are disappointing. The effect of prostacyclin appeared to be only transient [104 105]. The discovery that nitric oxide (NO) has a similar biological activity of endothelial-derived relaxing factor and as a dilator of smooth muscle has proceeded into a rapid introduction of NO into clinical medicine [106 112].
Experimental studies suggested a pivitol role of NO in the transitional circulation [113 114] Studies in which NO has been used as a rescue therapy in newborn infants with PPHN documented a reversal of ductal shunting due to a decreased pulmonary artery pressure and an increase of arterial oxygen pressure [107 109]. The response to NO may be dramatic and no adverse effects from NO have been reported so far, but not all infants respond to NO The application of NO in infants with CDH has been reported in case reports and small series. The results are inconsistent [108 110 112] Double-blind, randomized controlled clinical trials using nitric oxide in the treatment of PPHN are ongoing

1.4 Assessment of severity of disease and prediction of outcome in CDH

The complex nature of CDH, in which lung hypoplasia and persistent pulmonary hypertension may be present in varying degrees, hampers the quantitation of the severity of the disease. Many attempts have been made to define the severity of the clinical condition in order to identify the patients with the highest risk, to monitor the clinical course, to determine the need for more aggressive therapy, to predict outcome, to compare clinical studies and patient groups and to enable the evaluation of the efficacy of different treatment modalities [115 133].
Over the years several studies have been performed to predict outcome in babies with CDH based on the evaluation of arterial blood gases and pH [115 122] Boix-Ochoa stated that patients with initial pH values below 7.0 and paCO2 values above 100 mmHg had a bad prognosis and all died [116]. Mishalany used the arterial pH on admission to predict survival [117]. A pH > 7.2 was attended by a 100% survival. In patients with a pH between 7.0 and 7.2 on admission the survival chance was 50%, whereas the survival rate was only 11% for patients with an initial pH below 7.0 Raphaely and Downes used the alveolar- arterial oxygen gradient ($AaDO_2$) for prediction (see Table 2) survivors had a mean $AaDO_2$ of 260 mm Hg after surgical repair

Table 2 **Calculation of the alveolar to arterial oxygen pressure difference ($AaDO_2$)**

$$AaDO_2 = PAO_2 - PaO_2$$

in which:

PaO_2= arterial partial oxygen pressure which can be measured by a bloodgas analysis

PAO_2= alveolar partial oxygen pressure which can be calculated according to the "alveolar air equation" of Comroe, in which PAO_2 is substituted by:

$$PAO_2 = PiO_2 - PACO_2 \left(FiO_2 + \frac{1 - FiO_2}{R}\right)$$

in which:

- $PACO_2$ = partial alveolar carbon dioxide pressure
- PiO_2 = partial inspiratory oxygen pressure
- FiO_2 = fraction of inspired oxygen
- R = respiratory exchange ratio (mostly 0.8)

assuming that:

- the inspiratory partial carbon dioxide pressure ($PiCO_2$) is zero.
- the alveolar partial carbon dioxide pressure ($PACO_2$) is equal to the arterial partial carbon dioxide pressure ($PaCO_2$), supposing that there is an efficacious (artificial) ventilation.

and calculating PiO_2 as:

$PiO_2 = FiO_2 (Pbaro - PH_2O)$

in which:

- Pbaro = atmospheric pressure in mmHg
- PH_2O = vapour pressure (being 47 mmHg at 37 ^{0} C)

results in:

$$AaDO_2 = FiO_2 (Pbaro - PH_2O) - PaCO_2 \left(FiO_2 + \frac{1 - FiO_2}{R}\right) - PaO_2$$

and if FiO_2 = 1.0, in:

$$AaDO_2 = Pbaro - PH_2O - PaCO_2 - PaO_2$$

compared to a mean $AaDO_2$ of 614 mm Hg in nonsurvivors, whereas an $AaDO_2$ of greater than 500 mm Hg before operation indicates a poor prognosis (92% mortality)[115] Collins et al confirmed more or less these observations a preoperative $AaDO_2$ greater than 560 mm Hg and a postoperative $AaDO_2$ greater than 600 mm Hg characterize those patients who certainly would die despite maximal conventional therapy[53].Manthei et al reported that patients with an $AaDO_2$ greater than 500 mmHg both before and immediately after surgery did not survive [118] Bloss et al predicted outcome in dependence on paO2 change in response to postoperative tolazoline administration [119]. An intravenous test dose of 2 mg/kg tolazoline was given, if postductal paO2 values were below 50 mmHg on maximal ventilatory therapy. He found that patients with a paO2 increase greater than 100 mmHg survived, whereas all patients with a paO2 increase less than 20 mmHg died. Fair "responders" with a paO2 increase between 20 and 100 mmHg had an equivocal outcome. However in most studies concerning arterial bloodgas values and outcome the ventilatory circumstances were not mentioned (spontaneous respiration or mechanical ventilation) nor the sites at which the bloodgas samples were taken (pre- or postductally) Bohn et al connected $paCO_2$-values with a ventilation-index as a predictor of outcome: "Bohn-boxes" (see figure 1) [120].

The ventilation index (VI) reflects the intensity of artificial ventilation in terms of ventilatory

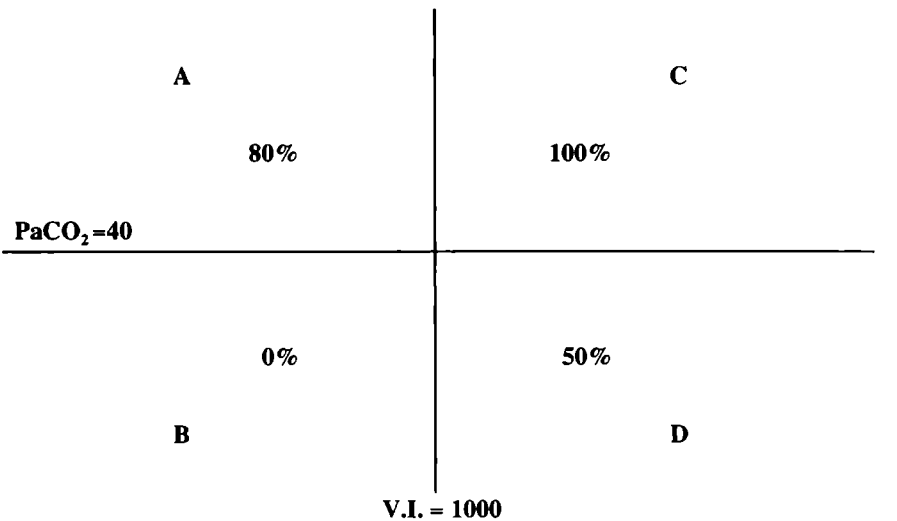

Figure 1 *Mortality risk for CDH , using bloodgas analyses and ventilator settings 2 hours after surgical repair, according to Bohn*
V I = ventilatory index = MAP x FiO_2

rate and airway pressure and was defined as VI = ventilatory rate x mean airway pressure. They found a (nearly) 100% survival in those infants, in whom normocapnia could be achieved with a VI lesser than 1000 (Box B)

Other authors distinguish "responders" and "nonresponders" for outcome-prediction, in which "responders" and "nonresponders" are defined by the ability or the inability to achieve a best postductal paO_2 ($BPDPO_2$) of 100 mmHg or more [121 122] O'Rourke et al reported that the mortality rate was 100% in a group of patients in which the paO_2 was consistently less than 100 mmHg (13,3 kPa) on a FiO_2 of 1 0, compared to a mortality rate of 23% in a group, in which at least one postductal paO_2 value was greater than 100 mmHg (13,3 kPa) [121]. In a study of Wilson et al it was shown that in patients with a $BPDPaO_2$ greater than 100 mmHg the survival was 91%, whereas the survival was only 7% when the $BPDPaO_2$ was less than 100 mmHg [122]

In a preliminary study Antunes et al speculated that the preoperative measurement of the functional residual capacity (by helium dilution technique) is a good indicator of pulmonary hypoplasia, better than the oxygenation index, and as a consequence a better predictor of outcome in CDH[133]. The measurement of preoperative pulmonary function tests (compliance and tidal volume) may be helpful to predict which infants will require ECMO[3]

Tracy et al suggested that a postoperative tidal volume of more than 4 mL/kg may be critical for survival[3].

Other attempts have also been made to use anatomic parameters for predictive purposes [123 132]. Using chest X-ray studies Touloukian and Markowitz drafted a preoperative X-ray scoring system for prediction of outcome [123]. If the stomach was located intrathoracically in leftsided defects the survival had been reported to be worse [124-126]. A large defect requiring a prosthetic patch closure has been associated with a worse outcome [127 129]. Right sided hernias appeared to have a poorer prognosis [82 130 131] Nielsen et al reporting on factors affecting survival mentioned only one survivor out of six patients with right sided defects [130]. Tibboel et al observed a 100% mortality in patients with right sided defects [131]

In other studies the time of diagnosis was considered to be of prognostic value [28 115 127 132]. Young ascertained that there is an inverse relationship between the age at diagnosis and the mortality [28]. If the clinical signs are so severe that a diagnosis of CDH is made within 24 hours after birth, the mortality appeared to be more than 50% (61%). An antenatal diagnosis of CDH was felt to imply a poor prognosis [19] Adzick et al found only 19 survivors out of 94 prenatally diagnosed cases (20%) despite optimal conventional therapy started immediately after birth The outcome for fetuses with prenatally detectable CDH and polyhydramnios is particularly dismal (89% mortality) [19].

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Chapter 2

Extracorporeal Membrane Oxygenation

2.1 Introduction

2.2 Performance of ECMO-therapy

2.2.1 Vascular Access for ECMO

2.2.2 Components of ECMO circuit

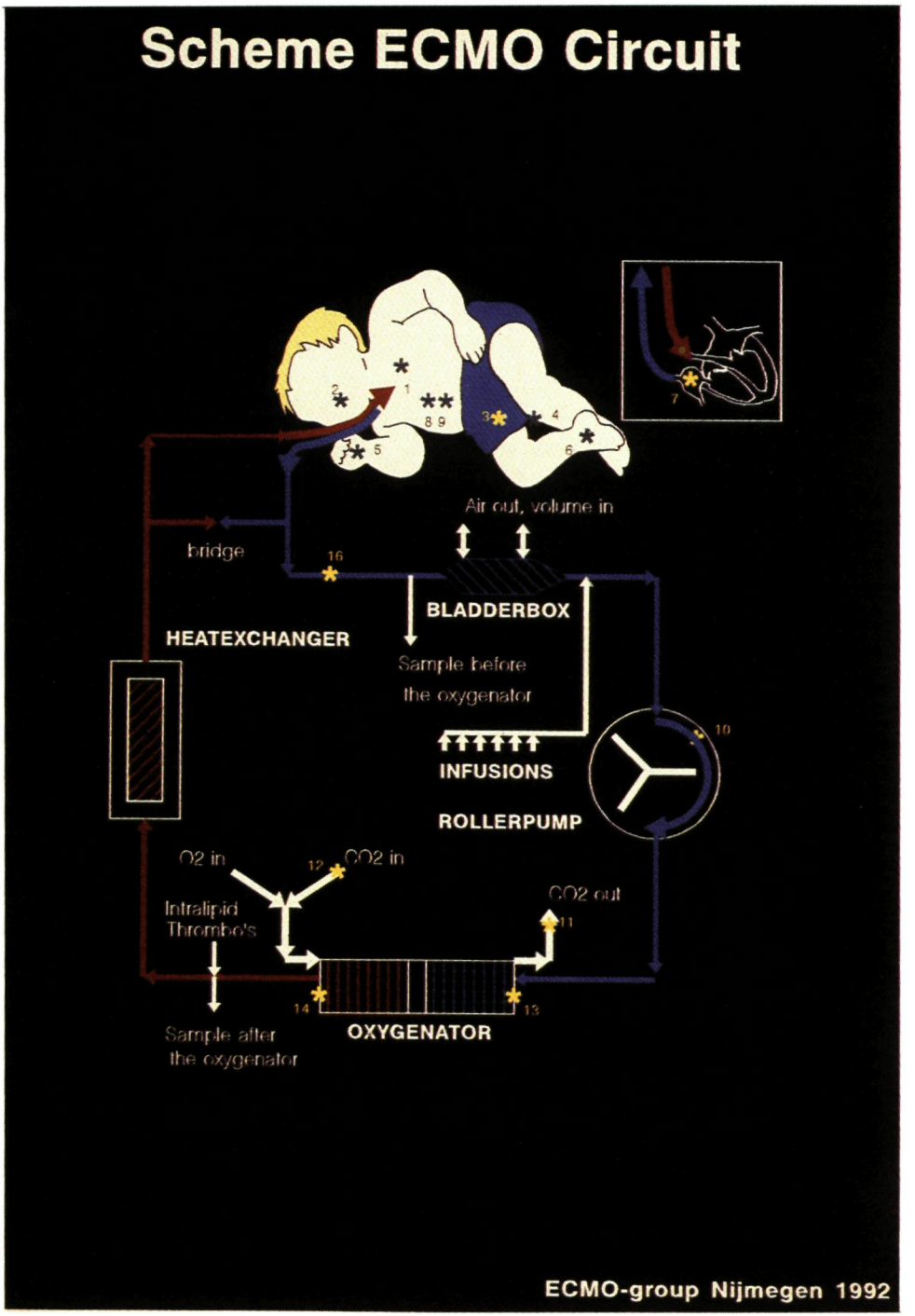
2.2.3 Daily Management of ECMO

2.3 Patient selection for ECMO

2.4 Complications during ECMO

2.5 Extra Corporeal Life Support Organization – Registry

Figure 1 *Scheme of VA-ECMO treatment*



2.1 Introduction

Extracorporeal Membrane Oxygenation (ECMO) is the application of temporary, but prolonged gas exchange outside the body by the use of extracorporeal circulation in patients with reversible life-threatening situations of cardiac and/or pulmonary failure[1-4]. (fig 1)
It is a last-resort-therapy for those patients who do not respond to maximal medical management including maximal mechanical ventilation and who are likely to die without ECMO in continuing conventional therapy. The use of this technique requires some type of anticoagulation (usually heparinization) to prevent clot formation, but consequently bleeding is always a potential complication[5,6].
Under a grant of Governmental Healthcare Authorities Extracorporeal Membrane Oxygenation was introduced into the University Hospital of Nijmegen for the treatment of respiratory failure in neonates – including infants with congenital diaphragmatic hernia – in 1991[7].
The most accepted method of ECMO – certainly in those days – was venoarterial ECMO (VA-ECMO)[1-4]. Because veno-venous ECMO was still in the experimental stages of development, VA-ECMO was adopted in our institution. In this introductory chapter general aspects of ECMO are briefly described according to our ECMO protocol, like ECMO-circuit, vascular access for ECMO, patient selection for ECMO, and complications of ECMO-therapy.

2.2 Performance of ECMO-therapy

2.2.1 Vascular access for ECMO

Before initiation of ECMO-therapy the ECMO system has to be attached to the patient (fig. 2). For that purpose cannulas have to be placed in the patient for high-volume blood flow.
In neonates the number of sites available for vascular access is limited[8].
Most frequently used is venoarterial bypass, for which cannulas are placed in the neck[1-4,8]. Via the right internal jugular vein blood is drained from the right atrium to the circuit.
Through a cannula in the right common carotic artery the blood is returned to the systemic circulation.
In our institution this procedure is performed in the Neonatal Intensive Care Unit.
Both vessels are ligated at the cranial site permanently. The cannulas are connected to the circuit, ensuring that no air bubbles enter the circuit or the patient.
To prevent bleeding from this operative site during bypass fibrin glue (Tissucol [R]) is installed into the wound before closure [9]. Cannula placement is confirmed by X-ray or more reliably by

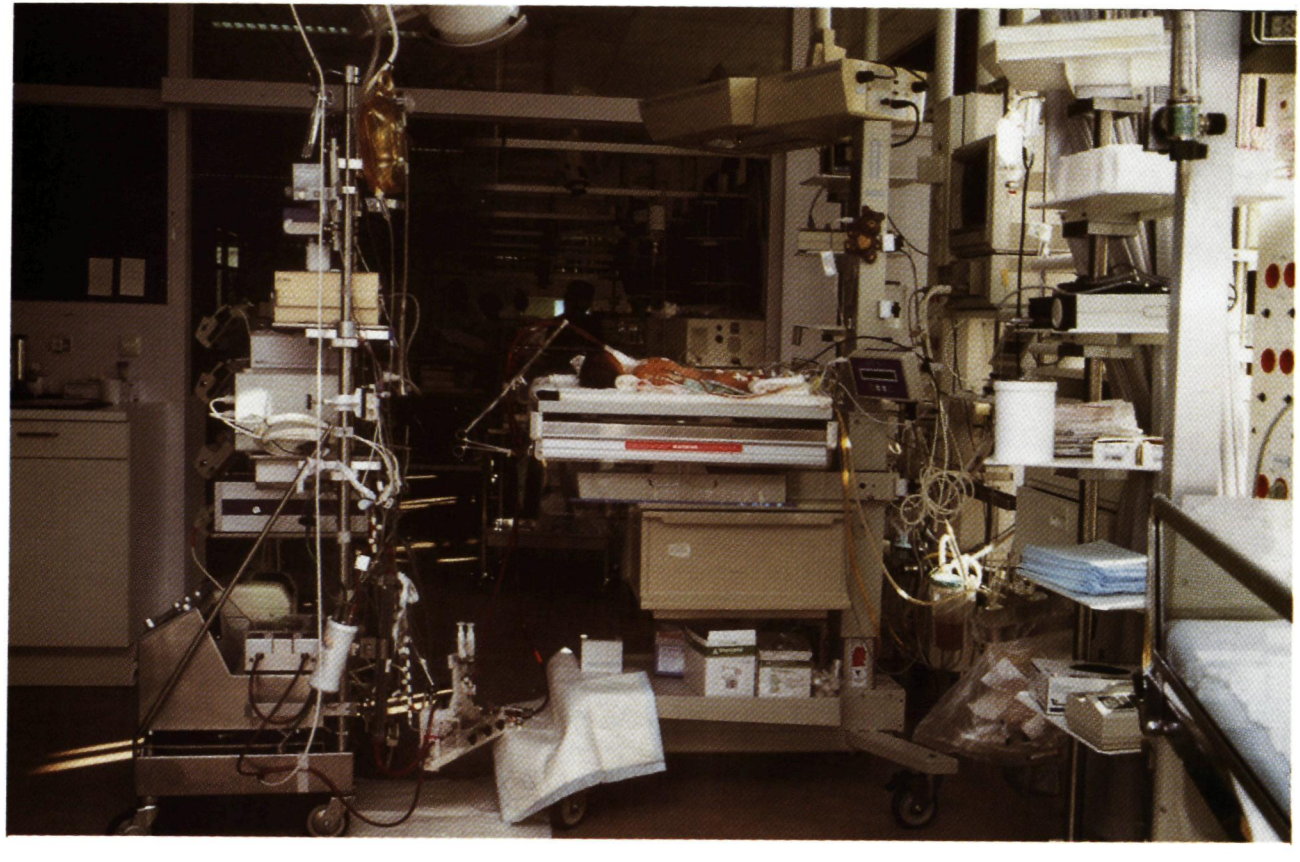


Figure 2 *Clinical performance of ECMO in the Neonatal Intensive Care Unit*

ultrasound [10]. The venous cannula should rest in the right atrium, and the tip of the arterial cannule shouls should be situated at the entrance to the aortic arch.
Controversy exists regarding permanent carotid artery ligation. Debates on the issue of whether the carotid artery should be ligated or repaired if the patient is decannulated are not completely closed[11-15]. Convincing arguments in support of carotid artery reconstruction have not been emerged yet.

2.2.2 ECMO-circuit

The ECMO system (circuit) consists basically of a blood pump, a membrane oxygenator, a heat exchanger, a tubing system and a servo-control module (fig 3).

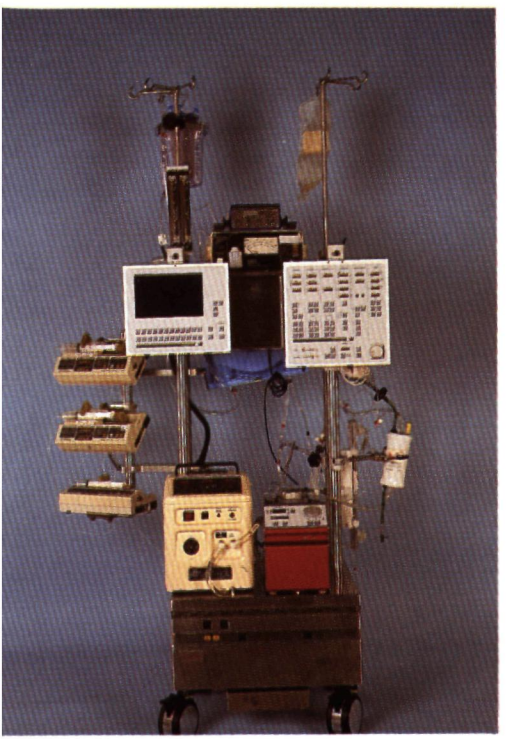


Figure 3 *Stand-by ECMO cart : completely prepared for clinical application (i.e. being in store for a maximal period of 4 weeks)*

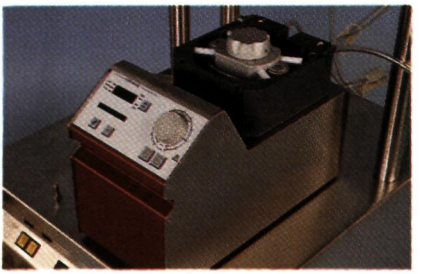


Figure 4 *The roller pump*

Figure 5 *The membrane lung*

The blood pump is a roller pump pushing blood through the membrane lung (fig 4). The membrane lung accomplishes carbon dioxide removal from and oxygen delivery to the blood (fig 5). It has 2 compartments divided by a gas permeable membrane with ventilating gas on one side and blood on the other. The heat exchanger rewarms the blood by a countercurrent circulating circuit of warmed water (fig 6).

The servo-control module consists of a small collapsible reservoir within the circuit (the bladderbox) with a sensitive microswitch resting on it (fig 7). If the reservoir collapses due to decreased volume of draining blood the roller pump is automatically turned off by the microswitch.

A broad variety of control modules are placed along the circuit. Pressure monitors are situated before and after the membrane lung. Sensors have been applied to the blood path to measure flow, temperature, hemoglobin saturation.

Before starting the ECMO procedure, the ECMO system is flushed with carbon dioxide that aids to remove air from the system and subsequently primed with cristalloid solutions, plasma and red blood cells. Acid-base balance and blood gases of the prime are adjusted appropriately[4, 16-18]. The prime volume of the ciruit is approximately 400 ml.

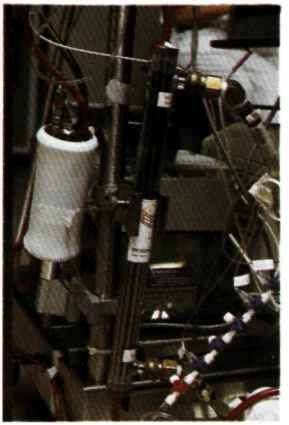


Figure 6 *The heat exchanger*

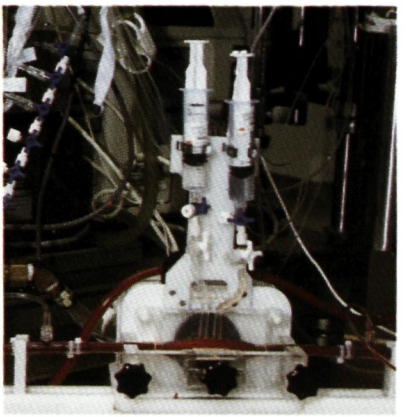


Figure 7 *The bladder box*

2.2.3 Daily Management of ECMO

Oxygenation After priming of the circuit, insertion of the cannulas and after connection of the circuit to the cannulas pump flow is started. Generally bypass can be established approximately 2 hours after the decision to ECMO support. Blood flows by gravity to the bladderbox and finally back to the patient by the roller pump. The amount of blood-flow is based on the degree of support required. At the beginning of a run the pump flow is gradually turned up until 80% of the infants cardiac output goes through the ECMO circuit (160 to 180 mL/kg/min, presuming 200 mL/kg/min as an average cardiac output) and/or good saturations (SaO_2) are recorded[1-4,17-19].

ECMO patients remain intubated and on the ventilator to prevent alveolar collapse, but at low pressure, low rate and low fractional inspired oxygen settings. ("rest"settings: FiO2 30%, rate 16 breaths per minute , PIP 20 to 24 mbar, PEEP 4 mbar).

Lung function of the infant is very poor the first 24 to 48 hours of ECMO. Typically the chest X-ray shows a pulmonary opacification ("white-out" of the lung)[20]. After 48 to 72 hours breath sounds improve, the chest X-ray shows increasing aeration and oxygenation is improving due to recovery of the lungs. Blood gases are monitored hourly. Patients oxygenation (measured by PaO2) is adjusted by increasing or decreasing bypass flow through the oxygenator, whereas the PaCO2 is adjusted by the flow and the mixture of gas (either oxygen or a mixture of oxygen and carbondioxide) flowing through the membrane lung.

The extracorporeal flow is set to maintain arterial oxygen pressure between 10 to 13 kPa. As the infant's lung function improves, additional oxygenation is taking place and the systemic

PaO2 increases above the level of 13 kPa, allowing to decrease the flow through the extracorporeal circuit ("weaning"). This weaning process continues gradually (10 to 20 ml/min per hour) until an ECMO flow of 50 ml/min is achieved with adequate bloodgases of the child (continuing with "rest" settings of the ventilator). Once these "idling" flows are reached and patient's condition remains stable for 6 to 8 hours with bloodgases within the normal ranges, the patient is removed from bypass and decannulated.

Heparinisation Systemic anticoagulation must be maintained during the ECMO-course to prevent clot formation[5,6]. Before cannulation a loading dose of 100 to 150 units of heparin per kg bodyweight is administered. This anticoagulation therapy is continued by a heparin maintenance dose of 20 to 50 units/kg/hour to the circuit. The heparin delivery is adjusted to maintain an activated clotting time (ACT) at 2 to 3 times baseline levels (220 to 250 seconds). The ACT is monitored every hour with an ACT-monitor (Hemochron^{R}).

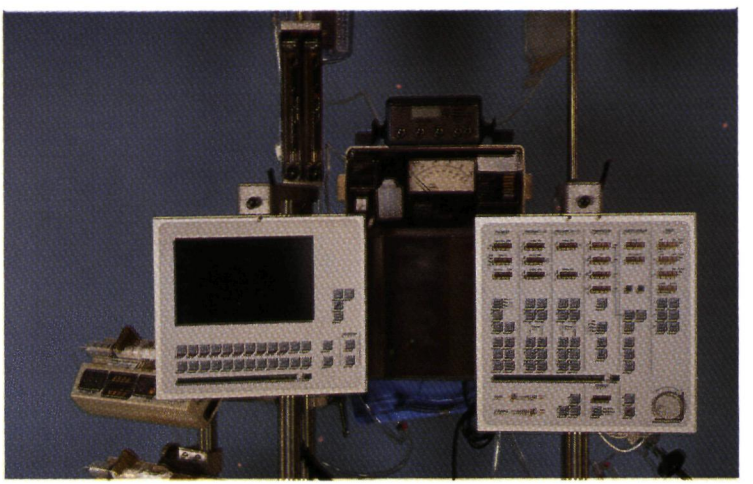


Figure 8 *Bed-side anticoagulation monitoring*

During ECMO extensive monitoring and frequent therapeutic adjustments are necessary to optimize oxygenation, ventilation blood pressure, anticoagulation and fluid balance.
Nutritional support is established by standard parenteral nutrition protocols. Prophylactic antibiotics (mostly ampicilline and gentamycin) are administered.
During ECMO the infant is kept slightly sedated. A combination of fentanyl and midazolam is mostly used.

2.3 Patient selection for ECMO

Because of the invasive nature of ECMO and the potential risks associated with the procedure, controversy exists regarding patient selection for ECMO application[21 23].

Two questions have to be answered

a Which patients can be treated and helped by ECMO treatment and,

b. When should ECMO be instituted?

From the experience with ECMO and based on known complications of ECMO several "general" criteria have emerged for the application of ECMO[21 27]

Important considerations before the initiation of ECMO concern the reversibility of the disease or the respiratory failure and the quality-of-life following survival with ECMO (Congenital) anomalies incompatible with quality life do not fit the neonate for ECMO therapy.

After a period of assisted ventilation lasting for 7 to 10 days the development of chronic lung disease may be presumed. Since ECMO is not able to reverse permanent pulmonary fibrosis, it is mostly not offered to a neonate, who has been ventilated for longer than 10 days

The requirement of systemic anticoagulation sets restrictions to the application of ECMO in neonates with major bleeding disorders or with a significant intracranial hemorrhage[28 31].

Because premature infants have significantly higher risks of intracranial hemorrhage, ECMO is recommended only for neonates weighing more than 2000 grams or being older than 34 weeks gestational age[31].

The major underlying cause of respiratory failure in newborns is persistent pulmonary hypertension (PPHN). PPHN is a reversible condition and an outstanding indication for ECMO treatment.Since ECMO provides good oxygenation it breaks the vicious cycle of PPHN, where hypoxia causes pulmonary vasoconstriction which causes right-to-left shunting, which continues the hypoxemia.PPHN is present in diseases such as meconium aspiration syndrome (MAS), congenital diphragmatic hernia (CDH), sepsis, perinatal asphyxia, and respiratory distress syndrome (RDS).

It is generally accepted, that ECMO should be instituted, when all methods of conventional therapy have been exhausted and when the mortality risk is 80% or more with continuation of conventional therapy[1 4 21 27]. However, both conditions are not well-defined.

Maximal conventional endeavours may vary from institution to institution Which treatment is included in maximal conventional therapy? The optimal conventional therapy is changing with time. The formerly advocated hyperventilation has been abandoned[23 32 33]. Newer techniques and therapies are now available such as high frequency ventilation , among which high frequency oscillation, nitric oxide, surfactant replacement therapy and liquid ventilation.

For the prediction of 80 to 100% mortality most institutions are using the alveolar-arterial oxygen difference ($AaDO_2$)[24,26], the oxygen index (OI)[25,34], or some other criterion, in which the oxygenation of the patient is registered as a function of ventilatory condition for a certain period of time[4,23,27]. Although these criteria seem to be very accurate and objective, these scoring systems do not work in all cases. So also more subjective criteria based on clinical judgment are added to the aforementioned criteria. All entry criteria are listed in table 1. Most centra have used historical controls to settle their criteria.

Table 1 **Criteria for ECMO treatment**

Gestational age > 34 weeks
Birth weight > 2000 grams
Reversible disease or cause of respiratory failure
Mechanical ventilation < 10 days
No major pathology incompatible with life
No major cardiac lesion
No coagulopathy or bleeding complications
No (major) intracranial hemorrhage

$AaDO_2$ > 610 mmHg for 8 hours*
$AaDO_2$ > 605 mmHg for 4 hours and PIP > 38 mbar*
Oxygen Index (OI) > 40 for 3 of 5 consecutive bloodgasanalyses**

Acute deterioration with pH < 7.15 and/or paO_2 < 5.3 kPa for 2 consecutive hours
Unresponsiveness to maximal therapy with pH < 7.40 and pO_2 < 7.3 kPa for 3 hours

Signs of barotrauma (presence of any four of the following):

- interstitial emphysema
- subcutaneous emphysema
- pneumoperitoneum
- MAP > 15 cm H_2O
- pneumothorax
- pneumopericardium
- persistent air leak for 24 hours

* $AaDO_2$=Patm - PH_2O - PaO_2 - $PaCO_2$, if FiO_2 = 1.0

** OI = MAP x FiO_2 x 100/PaO_2

Table 2 **Complications**

Patient complications

- Bleeding complications
  - intracranial (ICH)
  - pulmonary or gastrointestinal
  - cannule site or surgical site
  - disseminate intravasal coagulopathy (DIC)
- Neurological complications
  - brain death
  - seizures
  - cerebral infarction
- Cardiovascular complications
  - hypertension
  - hypotension and renal failure
  - myocardial stun
  - cardiac arythmia
- Metabolic complications
  - electrolyte disorders
  - hematologic (anaemia, thrombocytopenia)
  - renal
- Infectious complications

Mechanical complications

- Failure of devices
  - oxygenator
  - heat exchanger
  - pump
- Rupture or disconnections
  - raceway
  - tubing
  - connectors
- Embolization
  - air
  - clots
- Cannula problems
  - malposition
  - kinking

2.4 Complications during ECMO

Complications, problems or unexpected incidents during ECMO may arise in the patient or in the circuit and may be related to the primary disease, to the treatment on the whole or to technical aspects of the circuit in particular[28 29 35 46] Complications are listed in table 2. Bleeding complications due to systemic anticoagulation belong to the most serious and the most often occurring complications[28 31 35 37 43]. Intracranial bleeding is the most feared and is the most common cause of death Following surgical repair congenital diaphragmatic hernia patients can have significant bleeding requiring early removal from ECMO support. Other complications are related to embolization from the bypass circuit like clots, air or other kind of particles (for example aluminium)[35 42 43 46]. Infection is another risk associated with such invasive procedure, but has not proved to be a major problem. Technical and mechanical complications within the circuit are usually managed by changing the component part of the circuit

Table 3 **Survival of neonatal ECMO patients by diagnosis according to ECMO Registry Report of the Extracorporeal Life Support Organization** International Summary, january 1997

Diagnosis	Number	Percent survived
Congenital Diaphragmatic Hernia	2451	59
Meconium Aspiration Syndrome	4263	94
Persistent Pulmonary Hypertension	1598	82
Respiratory Distress Syndrome	1166	84
Pneumonia/Sepsis	1853	76
Air Leak Syndrome	49	69
Other	541	76
Total	11921	81

2.5 Extracorporeal Life Support Organization (ELSO)

In 1986, when the clinical application of ECMO was growing rapidly all over the world, existing ECMO centers decided to collaborate and to collect their experiences in a central database[41,47].

This resulted in a worldwide patient registry, in which nearly all active ECMO centers are participating under the auspices of Extracorporeal Life Support Organization (ELSO).

Table 4 **Patient Complications associated with neonatal ECMO according to the ELSO-registry report**
International Summary, January 1997

Patient Complication	Number	Percent reported*	Percent survived**
Intracranial hemorrhage			
by HUS	1563	13	50
by CT scan	453	4	83
Brain death	140	1	0
Seizures	1543	13	66
Other neurologic problems	479	4	70
Gastrointestinal hemorrhage	253	2	51
Surgical site bleeding	717	6	52
Cannule site bleeding	665	6	72
Hemolysis	1568	13	73
Other hemorrhagic problems	875	7	66
Need for dialysis/hemofiltration	1654	14	59
Cardiac arytmia	476	4	59
Systemic hypertension	1450	12	78
Infection	728	6	62

* percentage of the total number of reported neonatal cases
** percentage of the number reported with that complication

This registry, that has now been filed for approximately 12.000 neonatal ECMO patients, provides opportunities for studying patient selection criteria, complications, technical features of ECMO therapy and patient outcomes as well as for better understanding of diseases treated by ECMO and quality control.

Cumulative reports are prepared quarterly and annually by this ELSO-registry[43]. Overviews of the registry are sent to all participating centers. In this manner the ELSO-registry has pointed to standards for expected outcomes and complication rates, upon which an individual center can judge its results and can compare its experience to an international experience.

The data of the Registry may be very helpful for technological improvement and adaptations in the current equipment, for health care providers and government authorities in reference to resource planning.

Neonatal ECMO data summarizing survival rates by disease category are tabulated in table 3, whereas the patient and mechanical complications reported by participating centers are detailed in table 4 and 5.

Table 5 **Mechanical Complications associated with neonatal ECMO according to the ELSO-registry report**

International Summary, January 1997

Complication	Number	Percent reported
Clots in circuit	3243	27
Cannula problems	1252	11
Oxygenator failure	620	5
Pump failure	199	2
Tubing rupture	112	1
Heat exchanger malfunction	129	1

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Chapter 3

Study Outline

3.1 Aim of the study

3.2 Detailed objectives

3.3 Main features of the study

3.1 Aim of the study

This thesis was motivated by the ongoing and disappointing high mortality among neonates with Congenital Diaphragmatic Hernia In this patient group sufficient gasexchange cannot always be warranted even by optimal conventional ventilatory and pharmacological management either the patient dies, or the patient survives at the cost of severe damage to the lungs For selected patients extracorporeal membrane oxygenation (ECMO) seems to represent a good alternative for relief of the respiratory insufficiency with an improvement of survival and with a reduction of persistent lungdestruction Wide experience in ECMO-treatment has been gained in the United States of America As appears from the Extracorporeal Life Support Organization (ELSO) registry ECMO was offered to more than 12000 neonates suffering from respiratory failure with a final survival rate of 81% According to internationally accepted criteria the survival rate of those neonates should have been approximately 0 to 20% by continuation of conventional therapy without the use of ECMO
Preparatory to the definite introduction of ECMO in the Netherlands as approved by Health Care Authorities a study concerning the efficacy and the cost-effectiveness of ECMO was conducted This thesis reflects a part of the results of this study with regard to neonates with CDH who are judged irretrievable by conventional therapy
The main question concerns the impact of clinical application of ECMO therapy on the management of neonates with Congenital Diaphragmatic Hernia

3.2 Detailed objectives of the thesis

1 CDH patients selected for ECMO treatment had to have an expected mortality chance of 80 to 100 % if conventional treatment was continued The question is if it is possible anyway to assess the severity of the disease and to predict the outcome for CDH patients Can mortality reliably be predicted either by radiological examination (Chapter 4) or by alveolar to arterial oxygen pressure gradients (Chapter 5)?
2 Is ECMO therapy efficacious for CDH patients or in other words is it possible to improve the survival of CDH patients by the application of ECMO (Chapter 7)?
3 ECMO is an aggressive and invasive, potentially life-saving therapy The questions are with which features (Chapter 6) and with which adverse consequences (Chapter 8 and 9) the clinical introduction of ECMO therapy is attended
4 Beyond the effects at the short term – regarding survival and early complications- it might be wondered, what the effects at the long term are for CDH patients, who could be salvaged by ECMO (Chapter 10 and 11)

3.3 Main features of the thesis

The studies presented in this thesis are all clinical, patient-linked studies. The questions concerning mortality prediction were answered by a retrospective study. For answering the major question regarding the efficacy of ECMO an open prospective study-design was used with historical controls.
Starting ECMO as a project of developmental medicine with a grant of Governmental Health Care Authorities, it was decided to abandon a prospective randomized study.
Because literature reports mentioned improved survival in favour of ECMO and because ECMO only should be applied in neonates, who were very likely to die without ECMO, a randomized study was estimated to be misplaced scientifically as well as ethically.
The results of ECMO treatment were evaluated by comparing the survival of ECMO treated CDH patients with that of conventionally treated historical control patients with the same expected mortality and with the same in-and exclusion criteria.
For evaluation of the short-and longterm effects and the outcome a registry form and a follow-up protocol were drafted before the introduction and clinical application of ECMO. All complications were registered. The psychomotoric and physical development was recorded at one year of age, according to the previously appointed protocol.

Part II

Severity Assessment and Prediction of Outcome for Neonates with Congenital Diaphragmatic Hernia

Chapter 4

Is preoperative risk assessment of newborns with Congenital Diaphragmatic Hernia possible by means of chest X-rays?

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Abstract

Congenital diaphragmatic hernia (CDH) of the newborn constitutes an emergency. The overall mortality exceeds 50%. Touloukian and Markowitz described a preoperative X-ray scoring system for predicting outcome following repair of CDH. We reviewed the preoperative X-rays of 33 newborns with CDH according to this system All infants had to be operated within 24 h of age because of serious respiratory distress. Unlike Touloukian and Markowitz, we were not able to identify the survivors by this scoring system. A number of arguments are presented which may contribute to an explanation for this discrepancy. We conclude from our series and that of Touloukian and Markowitz that a preoperative pneumothorax and a diaphragmatic defect which cannot be closed primarily seem to constitute the only reliable unfavorable signs in emergency cases.

Introduction

Congenital diaphragmatic hernia (CDH) constitutes a major surgical emergency in the newborn. Prompt diagnosis and appropriate treatment are essential for survival. Because of disturbed cardiopulmonary function, the overall neonatal mortality in CDH exceeds 50% [3]. If patients with the highest risk can be identified preoperatively, they may be submitted to more aggressive management. Such management may comprise ligation of the ductus Botalli [1], prophylactic bilateral thoracic drainage, judicious postoperative artificial ventilation, and vasodilator therapy [5]. Even extracorporeal circulation with a membrane oxygenator may be considered [2].

Touloukian and Markowitz described a preoperative X-ray scoring system for risk assessment of newborns with CDH [6]. They reviewed the X-rays of 34 newborns with CDH through the foramen of Bochdalek, obtained before 12 h of age. Seven factors were graded, including:(1) side of diaphragmatic defect; (2) location of stomach in thorax or abdomen; (3) presence of a pneumothorax; (4) degree of mediastinal shift; (5) amount of visceral distention; and (6) relative volumes of aerated ipsilateral and (7) contralateral lung. There was no statistical difference in the degree of mediastinal shift or visceral distention in the surviving and non-surviving group. The scores assigned to each of the *five remaining* radiographic factors having a significant correlation with survival were summed to obtain a cumulative X-ray score (Table 1). Total scores ranged from 2 to 9. Twelve of 16 survivors (75%) scored 6 or less, whereas 16 of 18 non-survivors (89%) scored above 6. These results are highly significant ($P<0.005$). Mortality was 100% in 4 infants with a preoperative pneumothorax and 90% in 10 infants with a right-sided hernia.

Materials and methods

We reviewed preoperative chest X-rays of 33 newborn infants who were operated because of CDH through the foramen of Bochdalek during the first 24 h of life. All children were operated between 1969 and 1985 in the University Hospital of Nijmegen. Patients whose preoperative X-rays were not availabe were not included. All preoperative radiographs were reviewed by an unbiased observer who did not have knowledge of the clinical outcome. Only the final preoperative X-ray was used in calculating results. The criteria and grade assignments were identical to those described by Touloukian and Markowitz (Table 1).

Table 1 **Preoperative X-ray scoring system as described by Touloukian and Markowitz**

Criteria	Score
Side of diaphragmatic defect	
left	1
right	2
right with liver	3
Location of stomach	
abdomen	1
thorax	2
Pneumothorax (ipsilateral or contralateral)	
absent	0
present	2
Volume of aerated ipsilateral lung	
> 25%	0
< 25%	1
none	2
Volume of aerated contralateral lung	
normal to 75%	0
75 - 50%	1
50 - 25%	2

Results

Twenty patients were male, 13 female. Twenty of 33 patients (61%) survived. The preoperative X-ray score of five factors ranged in our series from 5 to 7 (Table 2). Thirteen of 20 survivors (65%) scored 6 or less, while 9 of 13 non-survivors(69%) scored more than 6. This difference between survivors and non-survivors was not statistically significant: $X^2=3.584$ ($0.05<P<0.1$). None of these five individual X-ray signs revealed significant differences between the two groups, nor were mediastinal shift and visceral distention associated with statistical differences between survivors and non-survivors. There were no cases with preope-

rative pneumothorax in our series. We also reviewed length of gestation, birth weight, and preoperative blood pH of the newborns with CDH. Length of gestation and birth weight did not differ between survivors and non-survivors. The difference in blood gas analysis between survivors and non-survivors was nearly significant ($0.05<P<0.10$) by chi-square analysis $X^2=5.595$ and df = 2). We were unable to close the diaphragmatic defect primarily in 8 cases so that some kind of a patch had to be used; none of the 8 patients survived.

Table 2 **Preoperative X-ray scores of our series**
The criteria and grade assignment are shown in table 1

Total score	Number of survivors	Number of non-survivors
2	-	-
3	-	-
4	-	-
5	4	-
6	9	4
7	7	9
8	-	-
9	-	-

Discussion

At present, the overall mortality of CDH still exceeds 50%. If patients with the highest risk can be identified preoperatively, they may be submitted to more aggressive management. Touloukian and Markowitz described a preoperative X-ray scoring system and found a highly significant difference between survivors and non-survivors [5]. We did not find such a difference. Since we had no difficulties in carrying out the scoring system, we do not think that differences in interpretation may be the cause of of this discrepancy. A number of disparities between their series and ours may contribute to an explanation.

First, the selection of patients in both series was different. In the series of Touloukian and Markowitz all first radiographs were taken before 12 h of age, so their group can include emergency cases as well as non-emergencies.

Since the aim of a scoring system should not be to differentiate between emergency and non-emergency, but rather to assess the risk of the emergency cases, we included only emergency

cases who had to be operated before 24 h of age.

Secondly, in the series of Touloukian and Markowitz there were 10 cases (29%) with a right-sided hernia, while in our series there were only 4 (12,5%). These right-sided hernias are known to have a poor prognosis.

Thirdly, we did not encounter a case with a preoperative pneumothorax, while Touloukian and Markowitz included 4 cases (12,5%), all of whom did not survive. Since this is not a normal feature of CDH, it reflects the necessity of forceful resuscitation for severe respiratory distress

The Woolf test of homogeneity for the association between score over 6 and survival among the patients in both studies was calculated as $X^2=2.074$ (df = 1 and $0.10 < P < 0.20$)[4]. Since this test is not significant, the results of both studies are, statistically speaking, not different.

In conclusion, we do not regard the X-ray scoring system of Touloukian and Markowitz to be as useful as they suggest It remains very difficult, if not impossible, to predict survival following repair of CDH The only reliable unfavorable signs in emergency cases seem to be a preoperative pneumothorax and a diaphragmatic defect which cannot be closed primarily.

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Chapter 5

Do we use the right entry criteria for Extracorporeal Membrane Oxygenation in Congenital Diaphragmatic Hernia?

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Abstract

In a retrospective review we analysed alveolar-arterial oxygen difference ($AaDO_2$) as an entry criterion for Extracorporeal Membrane Oxygenation (ECMO) in neonates with several forms of acute respiratory insufficiency. Although for meconium aspiration syndrome, respiratory distress syndrome, sepsis, and idiopathic pulmonary hypertension of the newborn we found values in accordance with the literature, patients with Congenital Diaphragmatic Hernia (CDH) met 80% mortality criteria with significant lower $AaDO_2$ values. Several patients died before ever reaching usual entry criteria for ECMO, because serious lung deterioration makes $AaDO_2$ values unreliable. Awaiting classical ECMO entry criteria for patients with CDH may at least partially explain the lower survival rate for ECMO in CDH.

Introduction

Experience in the Unites States and in Europe has proved the beneficial effect of Extracorporeal Membrane Oxygenation (ECMO) on survival in neonates with acute temporary (cardio-) pulmonary insufficiency, refractory to maximal conventional treatment[1]. Awaiting long-term evaluation, ECMO is still considered as a therapy of last resort, requiring 80% mortality predictions. Raphaely and Downes used the alveolar-arterial oxygen difference ($AaDO_2$) to predict outcome in newborns with congenital diaphragmatic hernia (CDH)[2]. Subsequently several authors have used $AaDO_2$ to predict mortality in other cases of acute respiratory insufficiency. Critical $AaDO_2$ values linked to time have been calculated in several analyses [3,4].

Despite overall good results of ECMO treatment in patients with several forms of acute temporary (cardio-)pulmonary failure, results in CDH are disappointing and the survival rates are significantly less than those in all other groups[1]. We hypothesized that these inferior results of ECMO in CDH, besides other reasons, could be explained by not using the right entry criteria.

Materials and methods

Calculating the 80% mortality risk for neonates of our group with acute respiratory distress, we analysed the files of 60 neonates with acute temporary (cardio-)respiratory insufficiency. This group consisted of 30 neonates treated in the neonatal intensive care unit between June 1989 and February 1990 for meconium aspiration syndrome, respiratory distress syndrome, sepsis, and idiopathic persistent pulmonary hypertension (pediatric group) and of 30 neonates treated in the pediatric surgical intensive care unit for CDH between January 1985 and May 1990 (CDH-group).

For all these patients we determined serial postductal $AaDO_2$s and calculated the $AaDO_2$/time span, that indicates the highest mortality with the best sensitivity and specificity. These calculations were done for the pediatric and CDH group separately. We used the method described by Beck et al in 1986[4].

Results

In the pediatric group 11 of the 30 patients (37%) and in the CDH group 17 of the 30 patients (57%) died

Table I shows the $AaDO_2$/time combination that predicts the highest mortality with the best sensitivity and specificity for both groups In both groups there was no significant difference between survivors and nonsurvivors concerning birthweight, gestational age, Apgar scores and other anomalies or complications The values for the pediatric group were in accordance with the literature In the CDH group most patients died before reaching classical ECMO entry criteria Using Beck's criterion ($AaDO_2 \geq 610$) sensitivity was only 47%, because 9 of the 17 deaths in the CDH group occurred before this criterion was met

In our CDH group the best ECMO entry criterion seems to be an $AaDO_2 \geq 520$ mmHg for 8 hours This includes nearly all nonsurvivors (sensitivity, 88%), and excludes most of the survivors (specificity, 85%)

Table 1 **Mortality risk in patient groups at published $AaDO_2$-time criteria**

		Mort	Sens	Spec
Pediatric group	$AaDO_2 \geq 520$ for 8h	58%	100%	58%
(n=30)	$AaDO_2 \geq 600$ for 12h	89%	73%	95%
	$AaDO_2 \geq 610$ for 8h	70%	64%	84%
CDH-group	$AaDO_2 \geq 520$ for 8h	88%	88%	85%
(n=30)	$AaDO_2 \geq 600$ for 12h	100%	41%	100%
	$AaDO_2 \geq 610$ for 8h	100%	47%	100%

Discussion

Mortality in CDH has remained virtually unchanged in spite of several important new developments. The availability of ECMO has given new expectations. Nevertheless the results of ECMO in CDH are a little disappointing and survival rates are significantly less than in all other ECMO indications[1]. This higher mortality can have several causes. CDH patients have not only pulmonary hypertension like other ECMO candidates, but have pulmonary hypoplasia and require major surgical intervention. It has been argued that serious lung hypoplasia is frequently present and many patients are irretrievable because of insufficient respiratory surface. In such cases survival of CDH will not improve with ECMO treatment.

Predictors of mortality in CDH are unreliable and the pulmonary hypoplasia cannot be measured in emergency circumstances. Several ECMO centers have tried to exclude patients with serious lung hypoplasia by asking for extra entry criteria, for instance a honeymoon period or at least one preductal or postductal PaO_2 of 80 to 100 mm Hg. Selection of patients with severe bilateral lung hypoplasia by these criteria is impractical because several other factors (barotrauma, fluid overload, preductal shunting) may play a role in the patients' deterioration. The use of a preductal or postductal $PaO_2 \geq 80$ or 100 mm Hg will improve the results but will exclude several babies from the benefit of ECMO[5].

In a retrospective review of ECMO deaths in CDH patients from the ELSO Central Registry data, Price et al showed that only 17% died of lung hypoplasia and 83% of the patients had a cause of death that was potentially reversible[6]. On the other hand the presence of hypoplasia makes the lungs more vulnerable to the deleterious effects of maximal conventional treatment, so that early ECMO could be more beneficial.

Our study showed that ECMO entry criteria may be different in CDH. It was proved that at least 53% (but probably even 100%) of the CDH patients would be selected too late for ECMO by adhering to the usual entry criteria (Table 1). In the calculation of $AaDO_2$ it is assumed that the $PACO_2$ equals $PaCO_2$ (Table 2).

Table 2 **Calculation of alveolar-arterial oxygen gradient**

$AaDO_2$	=	$PAO_2 - PaO_2$
PAO_2	=	$Pbaro - PH_2O - PACO_2$ (if $FiO_2 = 1,0$)
$PACO_2$	=	$PaCO_2$, if there is a good lung function
So: $AaDO_2$	=	$Pbaro - PH_2O - PaCO_2 - PaO_2$ (if $FiO_2 = 1,0$)

PAO_2	=	alveolar oxygen tension
PaO_2	=	arterial oxygen tension
Pbaro	=	athmospheric pressure
PH_2O	=	partial water vapor pressure
FiO_2	=	respiratory oxygen fraction

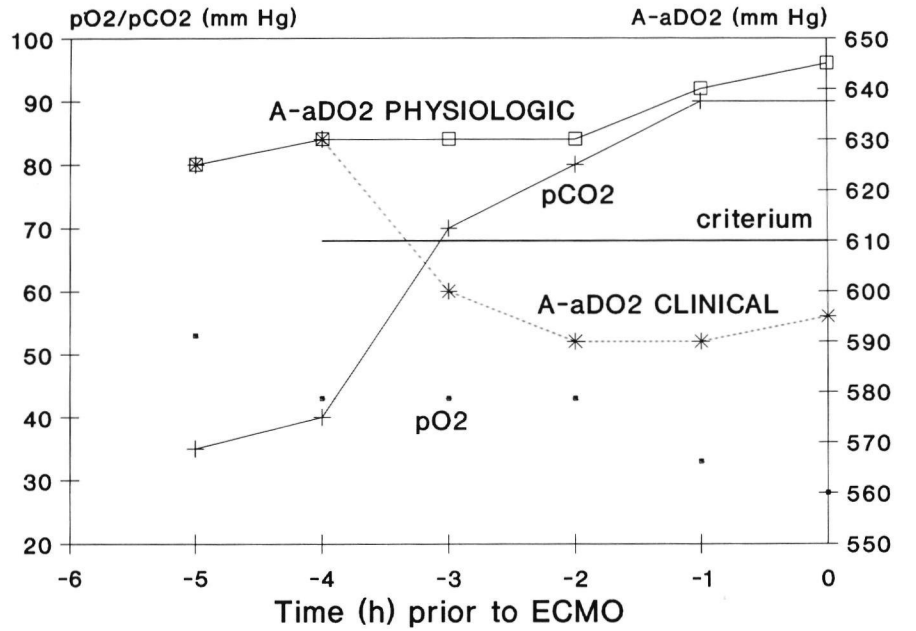

Figure 1 *The clinical calculated $AaDO_2$ drops below the ECMO entry criterion because the $PaCO_2$ increases while the clinical condition is getting worse. If physiological $PACO_2$ is substituted for actual $PaCO_2$, the patient is eligible for ECMO.*

In normal lung function this is a reasonable assumption, but this may not be correct in hypoplastic and damaged lungs, where $PACO_2$ can drop below physiological values, while the $PaCO_2$ increases. High $PaCO_2$ values have an adverse effect on the $AaDO_2$ calculations. The use of "classical calculated $AaDO_2$" may be misleading in CDH and may suggest improvement whereas in fact the baby is deteriorating (Fig 1). Therefore, we suggest that it would be better to calculate a physiological $PACO_2$ (40 mmHg) than to use the actual $PaCO_2$ value. We recalculated $AaDO_2$s for patients dying from CDH by substituting physiological $PACO_2$ for actual $PaCO_2$. In table 3 we compare "classical $AaDO_2$" with "physiological corrected $AaDO_2$" of these patients. Whereas according to "classical $AaDO_2$" 9 patients died before reaching ECMO entry criteria, if "physiological corrected $AaDO_2$" is used all 17 patients became eligible for ECMO.

Table 3 **$AaDO_2$ during 8 hours "classically calculated" and "physiologically corrected" in 17 patients with CDH, who died**

No	classical $AaDO_2$-8 h.	corrected $AaDO_2$-8 h.	arterial $PaCO_2$ (mmHg)
8	600-640	620-635	< 60
6	560-600	610-650	53-105
3	500-560	620-635	100-125

In conclusion it can be said that adhering to usual ECMO entry criteria may adversely influence outcome of patients with CDH and it should be realized that serious disturbance of lung function may make $AaDO_2$ values unreliable. Awaiting "classical ECMO entry criteria" for patients with CDH may at least partially explain the lower survival rate for ECMO in CDH. Therefore, we advise starting ECMO earlier in neonates with CDH, ie, at lower $AaDO_2$/ time levels or to use a "physiologically corrected $AaDO_2$" time combination as an entry criterion for ECMO.

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Part III

Extracorporeal Membrane Oxygenation in the treatment of Congenital Diaphragmatic Hernia

Chapter 6

Experience with Delayed Repair of Congenital Diaphragmatic Hernia during Extracorporeal Membrane Oxygenation in an European Center

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Abstract

In high-risk patients with congenital diaphragmatic hernia (CDH), we conducted a strategy of delayed repair following preoperative stabilization, including ECMO if necessary From January 1991 to July 1992, preoperative ECMO treatment was delivered to 6 out of 14 high-risk patients with CDH In this study, we report our experience with this policy of preoperative stabilization in six ECMO-treated patients in whom the diaphragmatic defect was repaired on ECMO In all patients bleeding complications occurred Three of the six ECMO-treated patients died, in two cases due to recurrent persistent pulmonary hypertension Overall mortality was 43%

Conceptual aspects of our approach are discussed Since the goals of our policy were not achieved, adjustments and renovations of the management protocol are discussed

Introduction

Mortality in newborn infants with congenital diaphragmatic hernia (CDH) who are symptomatic immediately after birth is still unsatisfactory despite all new developments in treatment Death can be due to severe pulmonary hypoplasia, to moderate pulmonary hypoplasia associated with persistent pulmonary hypertension (PPHN), or to recurrent PPHN after surgical repair In order to prevent respiratory and hemodynamic deterioration caused by PPHN postoperatively, several centers adopted a management protocol of preoperative stabilization and delayed repair of the diaphragmatic defect.
When extracorporeal membrane oxygenation (ECMO) routinely became available in our institution, we incorporated it in our management protocol to stabilize patients preoperatively if necessary. The aim of this study is to report our experience with delayed repair of CDH during ECMO treatment and to discuss some undecided questions in our strategy concerning CDH patients.

Materials and methods

Since ECMO became available in our institution (January 1991), we have used the following management strategy in high-risk CDH patients. Conventional treatment was initiated, consisting of (1) immediate endotracheal intubation and mechanical ventilation; (2) antibiotics; (3) nasogastric suction, (4) paralysis by pancuronium bromide, and (5) if necessary pharmacologic treatment with tolazoline, dopamine/dobutamine, or prostaglandin. After stabilization, the diaphragmatic defect was repaired. If necessary, ECMO was initiated postoperatively. Patients who were refractory to this maximal conventional support were preoperatively placed on veno-arterial ECMO. ECMO entry criteria for these patients are summarized in Table 1.
The methodology of veno-arterial ECMO has previously been described by Bartlett et al[1]. Heparin was continuously administered into the ECMO circuit to maintain the activated clotting times (ACTs) at 180-200 seconds. Platelets were infused to maintain counts more than 80 x 10^9/l. Once the hemodynamics and the patient's general condition had stabilized, the infant was weaned from ECMO to idling. As soon as weaning to idle was possible, surgical repair of the diaphragm was performed on ECMO in the Intensive Care Unit.
During and directly after surgery the ECMO flow was maintained at a high level during the

Table 1. **ECMO entry criteria for CDH**

1. $AaDO_2$ > 600 mm Hg for 8 h
2. PIP > 38 cm H_2O and $AaDO_2$ > 605 mm Hg for 4 h
3. OI > 40 for 3 h
4. Acute deterioration
   (pH < 7.15 and/or paO_2 < 40 mmHg for 2 h)
5. Failure to respond to maximal conventional treatment (paO_2 < 55 mmHg for 3 h)
6. Signs of barotrauma (four of the following)
   - interstitial emphysema – subcutaneous emphysema
   - pneumothorax – persistent air leak > 24 h
   - pneumopericardium – MAP > 15 cm H_2O
7. At least once a preductal paO_2 > 80 mmHg

$AaDO_2$= Alveolar-arterial oxygen differences O.I.= oxygenation index
PIP = peak inspiratory pressure MAP= mean airway pressure

first 24 to 36 hours, on the one hand to prevent a recurrent PPHN due to worsened thoracic compliance following repair[9], on the other hand allowing low ACTs to cope with bleeding complications. After this period of high ECMO flow the infant was weaned again to idle and finally decannulated. Conventional treatment was continued.

Results

From January 1991 to July 1992 we treated 14 neonates with high-risk CDH who were symptomatic at birth. Two infants died within 2 hours after birth despite immediate intubation and resuscitation. Six infants were operated upon after preoperative stabilization. One of these six patients died in the operating room and the remaining five could finally be weaned from the ventilator, but one of them required ECMO postoperatively because of recurrent PPHN. In six patients preoperative stabilization required ECMO treatment and these six patients underwent surgical repair of the CDH during ECMO.
The patient characteristics and clinical course of this latter group are depicted in table 2.

Table 2 **Characteristics of CDH patients treated by ECMO**

Results	Non-survivors				Survivors		
Patients No	1a	1b	2	3	4	5	6
Gestational age (weeks)	40	40	41	36	41	41	38
Hernia side (L,R)	L	L	L	L	L	L	R
Age at cannulation (h)	48	191	24	26	18	10	25
ECMO time prior surgery (h)	82	-	102	116	87	108	143
Patch repair	+	-	+	+	+	+	+
ECMO time after surgery (h)	36	-	60	101	54	73	92
Total time on ECMO (h)	118	87	162	217	141	181	235
Extubation (days after ECMO)	-	-	-	-	43	10	22
Complications:							
. hemorrhagic	+	-	+	+	+	+	+
. red blood cells (mL)	662	272	798	1215	455	800	900
. platelets (mL)	526	390	935	886	457	1250	467
. culture proven sepsis	+	-	-	-	-	-	-
. recurrent PPHN	+	+	+	-	-	-	-
Survival		no	no	no	yes	yes	yes
Death after decannulation (days)		15	10	0			

* 1 b designates second course of ECMO in the same patient

ECMO therapy was instituted 10 to 48 hours after birth (mean 25 hours). The duration of bypass ranged from 141 to 235 hours (mean 190 hours). Failure to wean from bypass because of severe pulmonary hypoplasia was not observed. Surgical repair was performed at age 118 to 168 hours after birth (mean 134 hours), after 82 to 143 hours on bypass (mean 109 hours) respectively. In all 6 patients the diaphragmatic defect was repaired with a Gore-tex^{R} prosthesis through an abdominal approach. In 1 patient the abdominal wall had to be closed with a Gore-tex^{R} patch. A chest tube was placed in all cases.
In all patients bleeding complications occurred at the surgical site, requiring 455 to 1215 ml of red blood cells (mean 850 ml) and 457 to 1250 ml of platelets (mean 818 ml). Therapy with ECMO was discontinued in one patient because of uncontrollable bleeding, but clinical deterioration forced us to return on bypass and recannulation 24 hours after decannulation. Postoperative ECMO bypass lasted for 36 to 147 hours (mean 85 hours).
Of the six infants, in whom ECMO was started after conventional therapy failed, three died (50%). Deaths were related to multi-organ failure in one patient and to recurrent PPHN in two patients, 10 and 15 days after decanulation. The overall mortality in the entire group was 43% (6 out of 14).

Discussion

Mortality remains high in neonates with high-risk CDH despite all new developments in treatment. The availability of ECMO has raised new expectations. Nevertheless, the results of ECMO treatment for CDH are somewhat disappointing and survival rates are significantly less for CDH than for all other neonatal ECMO indications (63% vs. 90%)[13].
Patients with high-risk CDH have not only pulmonary hypertension, like other ECMO treated infants, but concomitantly have pulmonary hypoplasia and require a major surgical intervention as well. Some patients have such severe lung hypoplasia, that they cannot survive, even with ECMO therapy. ECMO therapy should be avoided in these infants. It is thus important to determine the degree of hypoplasia prior to ECMO. However a reliable criterion or measuring method for adequate lung parenchyma is not available at this moment, whereas several other factors, such as barotrauma, fluid overload and preductal right-to-left shunting may contribute to hypoxemia as well[6]. Some centers added the presence of a "honeymoon" or the ability to ever attain a pre- or postductal PaO_2 of 80 or 100 mm Hg, to the existing ECMO entry criteria for CDH patients[12]. That may improve results, since the existence of sufficient lung capacity has been proved but will exclude babies from the potential benefits of ECMO. On the other hand hypoplastic lungs are more prone to the deleterious effects of maximal conventional therapy[7]. Therefore, the poorer outcome of CDH patients can also be related to long-overdue

ECMO treatment Many infants die from chronic lung disease (resembling bronchopulmonary dysplasia) after successful weaning from ECMO because they have been exposed too long to elevated airway pressures and oxygen concentrations before ECMO was started[7] A former study from our institution showed that ECMO entry criteria have to be adjusted and ECMO has to be initiated earlier in CDH patients[11]

In our series all patients could be weaned from bypass and no death was due to lung hypoplasia, so it seems, that hypoplasia was not a major problem in our group of ECMO-treated CDH patients. This probably has to do with the selection requirement of – at least once – a PaO_2 of 80 mm Hg. In an ELSO survey concerning ECMO, CDH and death pulmonary hypoplasia was the predominate cause of death in only 17% of the evaluated patients, whereas 83% of the infants had a cause of death that was potentially reversible[8]. Among those, PPHN was a major cause of death in ECMO-treated CDH patients (25%)[8]

In order to cope with the problem of PPHN, the strategy of delayed repair and preoperative stabilization was drafted in the management of CDH-patients[3,4,16] Up to now, this concept has not led to a significant decrease in mortality, but has also not affected overall mortality This approach enables not only selection of patients, but also enables electively scheduled CDH repair. In 1988 we adopted this policy of delayed repair for CDH patients, and when ECMO became available at our institution, we incorporated ECMO into our strategy of preoperative stabilization.

If preoperative stabilization requires ECMO, we have to deal with the question of the best time to repair the diaphragmatic defect. There are two alternatives for surgical intervention during or following ECMO support. If we operate during ECMO, recurrent PPHN – elicited by the surgical procedure and the consequently diminished thoracic compliance[9] – can be controlled by ECMO, but a high risk at hemorrhagic complications is introduced. If we operate following ECMO, we can preclude bleeding complications due to heparinization, but the ability to influence recurrent PPHN has been restricted. We decided to repair the defect on ECMO late in the ECMO course, when the patient had been shown to be weanable from ECMO. In this concept, PPHN as a result of the surgical procedure could be precluded or faced by ECMO support and in case of hemorrhagic complications, ECMO could be withdrawn within 1 or 2 days. During surgery we avoided major dissections and incidental procedures (eg. Ladd's procedure or appendectomy) because of heparinization. For the same reason, we used running sutures and prosthetic patches, which are also advantageous for the compliance [2]. By running high ECMO flows during and directly following surgical repair we try to not only prevent PPHN, but at the same time to preclude bleeding , since high ECMO flows allow low ACTs.

Despite all these measures, all our patients had significant bleeding at the surgical site,

requiring an average amount of 850 ml RBC and 818 ml platelets. In addition, we still encountered PPHN, even some time after ECMO discontinuation. Ultimately two infants died from PPHN, 10 and 15 days following decannulation.

Therefore, neither bleeding complications nor recurrent PPHN were prevented by this approach. In view of this experience, our strategy must be adjusted. One option is to prevent hemorrhagic complications, whether by the use of aprotinin[5] or aminocaproic acid[15], the use of a Cameda-heparin bounded circuit after surgical repair[10] or to abandon systemic heparinization entirely and at the same time renew the ECMO circuit[14] following surgery.

The other option is to postpone diaphragmatic repair after completion of ECMO support and decannulation[16]. If PPHN occurs following surgical repair and is again refractory to the conventional therapy, we have to consider reinitiating ECMO. However, ECMO is not a therapy for pulmonary hypoplasia, so does it make sense to return to ECMO at all? And if so, how much time may pass after which a second ECMO course will still be meaningful? If ECMO support is instituted a second time, we have to recannulate the infant. How many days following decannulation are we able to recannulate? How much risk of tromboembolic complications do we encounter? Moreover, has the patient to meet the same entry criteria? Do the same exclusion criteria apply to the second course?

So far, we have carried out a second ECMO course in one patient. Because of uncontrollable bleeding the first ECMO-run was discontinued 36 hours after surgical repair of the diaphragm. Clinical deterioration due to PPHN forced us to reintroduce ECMO support. Meanwhile the bleeding had stopped At recannulation we removed clots from the internal jugular vein by a Fogarty catheter. After reheparinization bleeding did not recur again. Ultimately, this patient died from PPHN 15 days following the second decannulation. In retrospect, was it a good decision to go on ECMO for a second course?

The best approach will await more experience.

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Chapter 7

Improving survival for patients with high-risk congenital diaphragmatic hernia by using extracorporeal membrane oxygenation

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Abstract

The benefit of extracorporeal membrane oxygenation (ECMO) in cases of high-risk congenital diaphragmatic hernia (CDH) was studied by comparing pre-ECMO (1987-1990) and post-ECMO (1991-1994) 3-month survival statistics. Fifty-five CDH patients who presented in respiratory distress within 6 hours after birth, were referred – 18 in the pre-ECMO era and 37 in the ECMO era.

During the entire study period (December 1987 through July 1994) the patients were treated by the same protocol of preoperative stabilization and delayed surgery; the only difference was the addition of ECMO beginning in January 1991. The patients were stratified based on the response to conventional treatment: 1, no response (irretrievable); 2, stable; 3, unstable. The 3-month survival for the unstable neonates (who could not be stabilized by conventional therapy) improved from 0% (0 of 9) in the pre-ECMO era to 61% (11 of 18) in the ECMO era ($p = 0,004$). This highly significant difference shows that ECMO is a very valuable addition to the management of high risk CDH patients whose conditions remain unstable despite maximal conventional therapy.

Introduction

Despite advances in neonatal care, including prenatal diagnosis, neonatal transport, intensive care treatment, anaesthesiology and surgery, the mortality rate among infants with congenital diaphragmatic hernia (CDH), treated by conventional ventilatory management and pharmacological support, remains high. The reported mortality rate for high-risk patients who have symptoms within 6 hours after birth ranges from 29% to 80% [1 9] Extracorporeal Membrane Oxygenation (ECMO) was introduced as a therapy for newborns with respiratory failure unresponsive to maximal conventional treatment and may be used to support neonates who have respiratory distress caused by CDH. [10-12]

A number of investigators have reported success in treating CDH with ECMO. [2 4 13 16] However, others have not seen improvement with use of ECMO [17 18]

According to the Extracorporeal Life Support Organization (ELSO) registry, the survival rate for CDH patients, treated by ECMO, is 58%.[19] This suggests that ECMO has no significant impact on the survival of newborns with high risk-CDH.

In the present report we evaluate the role of ECMO in the management of CDH at our institution.

Materials and Methods

All patients with CDH who were symptomatic within 6 hours after birth and who were referred between December 1987 and July 1994 were included in the study. All patients were treated by a protocol of delayed surgery after preoperative stabilization.[5 8]

When ECMO became available in our institution (in January 1991), it was incorporated into this protocol for CDH, whether preoperatively or postoperatively. ECMO was offered after conventional ventilatory and medical management had failed, if the patient fulfilled the entry criteria for ECMO, if there were no contraindications for ECMO and if parental consent was obtained. No infant in this study was excluded from ECMO support on the basis of failure to achieve a minimum PaO_2 before the institution of ECMO.

Venoarterial ECMO was used as previously described by Bartlett et al. [12] If ECMO was required for preoperative stabilization, the diaphragmatic defect was repaired during ECMO, at the end of the ECMO run, if the patient could be weaned from ECMO-support. [20] ECMO was discontinued, when respiratory failure resolved (gas exchange requiring PIP of less than 30, ventilator rates of less than 40 and FiO_2 of less than 0,50) or when a complication arose that required cessation of ECMO (such severe bleeding complications rendering a contraindication to continued heparinization) Survival is defined as "alive at the age of 3 months".

Survival statistics were compared for two time periods

(1) December 1987 through December 1990, when ECMO was not available and all children were treated with conventional ventilatory support and pharmacological management (the pre-ECMO era, n=18) and

(2) January 1991 through July 1994, when ECMO was available and was used, if conventional treatment failed (the ECMO era, n=37).

The children were classified into the three groups described below.

"Irretrievable" Patients. These patients were (1) newborns with severe respiratory distress, noted immediately after birth, in whom a reasonable or normal gas exchange was never reached, despite endotracheal intubation and artificial ventilation and who died within 2 hours after birth, before ECMO could be initiated (2) newborns who died before or during transportation (pre-ECMO era n=1,ECMO era n=7) or (3) newborns with severe congenital anomaly (especially chromosomal), for whom not all therapeutic modalities were offered (pre-ECMO era n=1).

Conventionally stabilized Patients These were newborns with high-risk CDH, who recovered well by (maximal) conventional treatment and who underwent surgical repair of their diaphragmatic defect after conventional stabilization. They never met ECMO-entry criteria before repair of their diaphragmatic defect (pre-ECMO era n=7, ECMO era n=12).

Unstable Patients. These were newborns with high-risk CDH, and who could not be stabilized by maximal conventional treatment and who met one or more ECMO-entry criteria (pre-ECMO era n=9, ECMO era n=18). The patients in this category were subdivided into those who did (a) or did not (b) receive ECMO support.

We made this stratification because we wanted to evaluate the effect of ECMO on survival. The irretrievable patients were in such distress that ECMO could not be initiated before death or before severe brain damage had occurred. In these circumstances any therapy, which ever applied, is doomed for failure. The availability of ECMO equipment had no effect on survival, neither in this group nor in the group of conventionally stabilized patients. Because no patient in the latter category met the ECMO-entry criteria and nearly all patients survived, ECMO is not a therapeutic option for this group. Thus, only in the unstable patients could the effect of the availability of ECMO equipment be measured.

For comparisons of survival rates, the two-sided Fisher's Exact test was used.

Results

Fifty-five newborns with high-risk CDH were evaluated, – 18 in the pre-ECMO era (Fig. 1) and 37 in the ECMO era (Fig.2).

One patient in the pre-ECMO era was categorized as "irretrievable" because of a chromosomal anomaly. One neonate in the first period and seven in the latter period were irretrievable; they died of severe respiratory distress shortly after birth, before ECMO could be or could have been initiated. In this category, the average transcutaneous oxygen saturation was 64%, the average PaO_2 4,5 kilo-Pascals (kPa) (34 mm Hg), the average $PaCO_2$ 10,9 kPa (82 mm Hg) and the average pH was 6,89.

In the pre-ECMO period, preoperative stabilization could be achieved by conventional treatment (CT) in seven patients (Fig. 1). In these patients the diaphragmatic defect could be repaired, and six survived.

Figure 1. **Progress of 18 High Risk CDH patients in the pre-ECMO era** (december 1987 through december 1990)

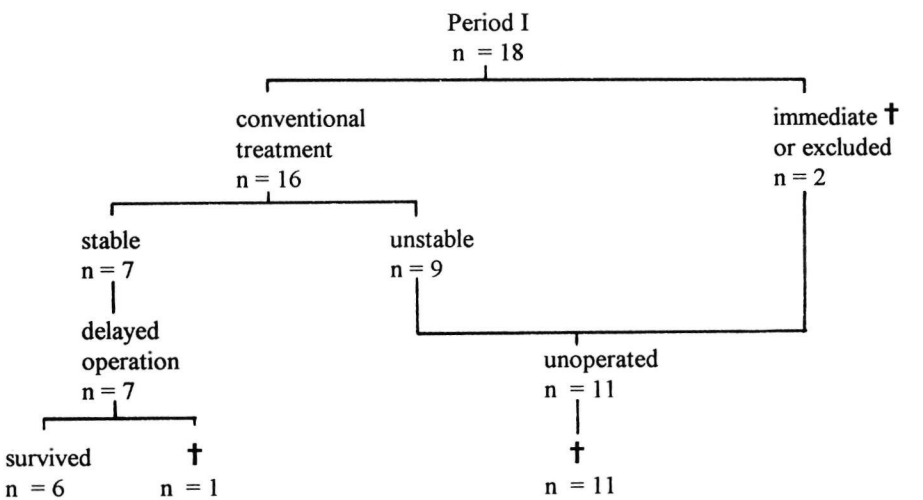
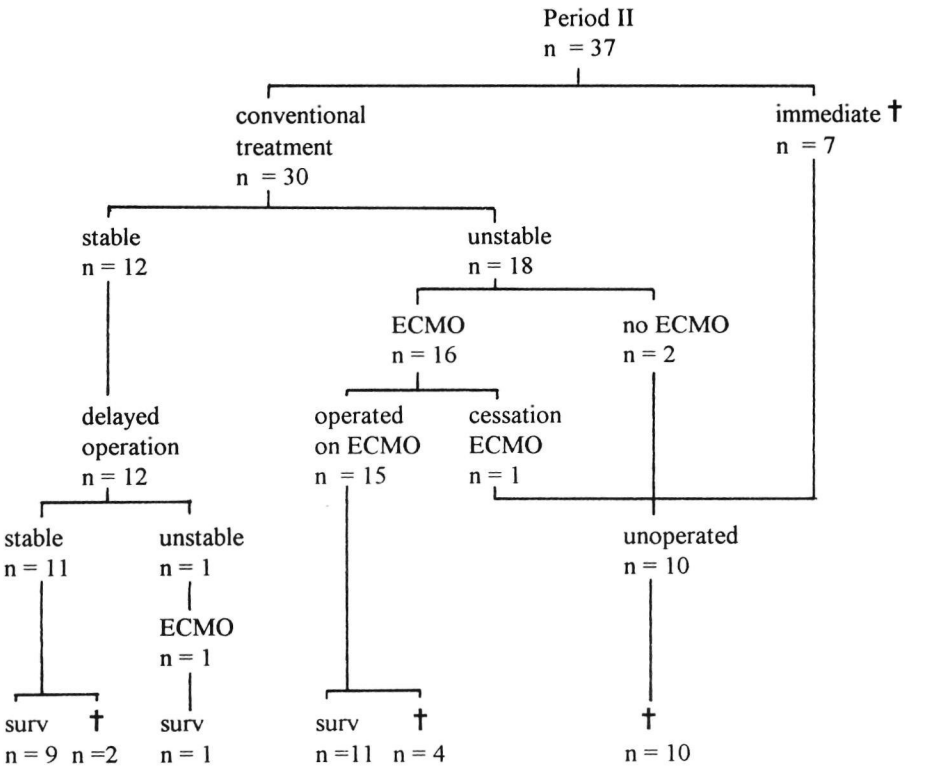


Figure 2. **Progress of 37 High Risk CDH-patients in the ECMO era** (january 1991 through july 1994)



Nine patients could not be stabilized conventionally; none of them had surgical repair, and none survived. These patients would have qualified for ECMO support had it been available. Since ECMO became available at our institution, preoperative stabilization by conventional therapy could be achieved in 12 patients (Fig. 2). All 12 had repair of their diaphragmatic defect, and 10 survived, although postoperative ECMO support was required for one of them. Eighteen cases were refractory to conventional management and were considered for ECMO-treatment. In two of the patients, ECMO therapy was not instituted; in one patient ECMO treatment was refused by the parents, and in the very first patient, who was an ECMO candidate, we thought it was better to repair the diaphragmatic defect before initiation of ECMO, during preparation of the ECMO-circuit. Both patients died. Thus, in 16 patients ECMO was used for preoperative stabilization. In one patient the ECMO treatment was discontinued

Table 1 **Demographic data for both time periods: pre ECMO era (Dec 87 through Dec 90) and ECMO era (Jan 91 through July 94).**

	Irretrievable		Conventionally stable		Unstable	
	pre-ECMO	ECMO era	pre-ECMO	ECMO era	pre-ECMO	ECMO era
male female ratio	0 2	4 3	3 4	5 7	5 4	10 8
gestational age (wk)						
average	42,0	38,7	38,5	38,0	40,3	39,8
range	(42-42)	(36-42)	(34-41)	(34-42)	(38-42)	(34-42)
birth weight (g)						
average	2850	2740	2780	2660	3160	3410
range	(2300-3400)	(1500-3460)	(1480-3500)	(1760-3740)	(2450-3930)	(2560-4175)
Apgar (average & range)						
1 min	1,5 (1-2)	1,8 (1-4)	7,4 (4-9)	5,0 (3-9)	4,5 (1-9)	3,2 (0-6)
5 min	2,5 (1-4)	3,8 (2-6)	6,0 (4-9)	6,7 (4-10)	4,8 (1-8)	4,8 (0-8)
side						
left right	2 0	5 2	5 2	10 2	8 1	16 2

because of severe cerebral bleeding and the patient died without having repair of the diaphragmatic defect. The other 15 patients could be weaned from ECMO, and all had repair of their diaphragmatic defect during ECMO, late in the ECMO run. Eleven survived. The four deaths after ECMO were related to multiorgan failure (n=1), severe lunghypoplasia (n=1), or recurrent persistent pulmonary hypertension (n=2) The demographic data of the different patient groups, for the two time periods, are reported in Table 1.
The overall survival was 33% in the pre-ECMO era and 57% in the ECMO era. Excluding the irretrievable patients in both periods the survival rate was 38% in the first period and 70% in the second period (Fisher's Exact test, p=0,08). The survival rate among infants who could be stabilized conventionally was 86% in the pre ECMO era and 83% in the ECMO era (Fisher's Exact test, p>0,50). The survival rate for the conventionally not-stabilized patients was 0% in the first period and 61% in the latter period (Fisher's Exact test, p=0,004).
Ultimately, 11 of the 16 unstable patients who were supported by ECMO survived (69%), whereas no unstable patient survived without ECMO support (Fisher's Exact test, p=0,0006).

Discussion

In this report we present our experience with 48 severely afflicted infants with CDH, who were treated according to a protocol of preoperative stabilization and delayed surgery [5 9] This protocol was unchanged during the entire period of the study.
The only difference in management was the addition of ECMO for (pre- or postoperative) stabilization since January 1991. This offers the opportunity to evaluate the role of ECMO in the treatment of high-risk CDH, by dividing the patients into two groups with respect to ECMO availability (pre-ECMO and ECMO era).
The overall survival rate for high-risk CDH patients increased from 33% in the pre- ECMO era to 57% in the ECMO era. This means improvement, but the difference is not significant statistically. For this reason, and because infants with CDH have gained less advantage by ECMO than have infants with respiratory distress from other causes [19], the benefits of ECMO support for high-risk CDH patients remain controversial. [2 4 13 18] However, to assess the impact of ECMO we must compare identical populations with respect to demographic data as well as severity of disease, because differences in the composition of the groups can influence the outcome.

Over the past decades many attempts have been made to grade the seriousness of the disease and to establish criteria by which survival could be predicted or by which patients could be considered for a certain kind of (aggressive) therapy.

Parameters used, are the interval from birth until the appearance of symptoms, the occurrence of a "honeymoon period" [21], and bloodgas analysis with and without linkage with ventilator settings and time, eg, $AaDO_2$, oxygenation index, ventilation index linked with $PaCO_2$ [9 22 28] Nevertheless, all criteria appear to be unreliable, there is no single, simple objective criterion by which the clinical course and outcome can be predicted and by which the two interrelated pathophysiological mechanisms (lunghypoplasia and pulmonary hypertension) can be unraveled.[4 14-16 28 31] In the literature there is agreement that neonates who are in respiratory distress within 6 hours after birth constitute a high-risk group. We divided this high-risk group in three subgroups, based on the clinical course at the time (maximal) conventional treatment was applied.

Some patients are considered to be irretrievable because they are unable to attain satisfory oxygenation despite maximal conventional therapy immediately begun after birth. These patients have not even the ability to meet standard ECMO criteria because of lack of time. They die before ECMO can be initiated. Most investigators report only a few such cases, but these comprise 19% of the CDH patients referred to our institution in the ECMO era. This group reflects the impact of the availability of ECMO on referral patterns, but this group has a negative influence on the overall survival rate, which can lead to misinterpretation of the efficacy of ECMO treatment in CDH patients. The amount of functional lung tissue in these infants is inadequate for survival. Since January 1991, 14 infants were transferred, pre- or postnatally, specifically for ECMO. Two could be treated conventionally, nine received ECMO support and three died before ECMO could be initiated.

In other patients, respiratory distress can be alleviated by immediate applied conventional therapy. Some such patients can be stabilized by conventional ventilatory management and never meet ECMO-entry criteria. Others cannot be stabilized conventionally and meet standard ECMO criteria. Only in this latter group of patients can a reliable judgment be made of the benefit of ECMO for CDH.

In both periods the conventionally stabilized patients and the unstable patients were comparable with respect to gestational age, birth weight, gender distribution, Apgar scores and side of the defect (Table 1). As might be expected, the survival rate of category II patients was virtually the same in both time periods – 86% in the pre-ECMO era and 83% in the ECMO era. However, the survival rate for unstable patients is significantly better in the ECMO era than it was beforehand (61% versus 0%). Because the groups are comparable for both time periods, and because the only difference in treatment is the addition of ECMO in the latter

period, the better survival rate can be attributed completely to ECMO therapy.
All children who survived after stabilization with ECMO, represent an increase in survivalrate. All unstable children, who met ECMO entry criteria died without ECMO support.
The fact that all children who met ECMO criteria died without ECMO support is in accordance with the aim of ECMO as a treatment of last resort, ie, only applied in critically ill infants, whose projected mortality rate was more than 80%
From the experience with high-risk CDH patients treated in our institution by a protocol of delayed surgery after preoperative stabilization, with and without ECMO, we draw the following conclusions:

(1) The overall mortality of high risk CDH patients is still high.
(2) Some infants have such severe lung hypoplasia that they were unable to attain sufficient gas exchange to bridge the time until initiation of ECMO.
(3) Use of ECMO support is an improvement in our therapy protocol for cases that cannot be stabilized by conventional treatment, the survival rate associated with ECMO (61%) is significantly better than that without ECMO (0%).
(4) ECMO availability changed the referral pattern, increasingly sicker patients are seen, who previously would not have survived.

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Complications and pitfalls in the treatment of Congenital Diaphragmatic Hernia

Chapter 8

Surgical Repair of Congenital Diaphragmatic Hernia during Extracorporeal Membrane Oxygenation
Hemorrhagic Complications and the Effect of Tranexamic Acid

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Abstract

Extracorporeal membrane oxygenation (ECMO) was incorporated in a strategy of delayed repair of congenital diaphragmatic hernia (CDH) and was used for preoperative stabilization in patients who were unresponsive to maximal conventional treatment. If ECMO was required for preoperative stabilization the diaphragmatic defect was repaired while the patient was on ECMO In the early experience with this approach all patients suffered from bleeding complications. Therefore, we adopted the use of antifibrinolytic therapy with tranexamic acid (TEA) during and immediately after CDH repair on ECMO.

The efficacy of TEA was studied in an unblinded study using historical controls by comparing the postoperative blood loss and the transfusion requirements of red blood cells (RBC) in patient groups treated without (n=9) and with TEA (n=10) Patients who received TEA had significantly less bleeding at the surgical site than patients not receiving TEA (57 v 390 mL, p=0.005) and had significantly lower RBC transfusion requirements than patients not receiving TEA (1.13 v 2 95 mL/kg/h, p=0 03). In the very first two patients of the TEA group we encountered fairly severe thrombotic complications. TEA may have contributed to those complications. Based on the authors' experience they conclude

(1) TEA is effective in reducing postoperative blood loss, hemorrhagic complications and RBC transfusion requirements associated with CDH repair on ECMO.
(2) TEA may be responsible for thrombotic complications.
(3) The appropriate, empirically established, dosage and administration pattern of TEA for CDH repair during ECMO seem to be one bolus of 4 mg/kg TEA intravenously 30 minutes before the anticipated CDH repair and a continuous infusion of 1 mg/kg/h TEA during the 24 hours after CDH repair.

Introduction

Since extracorporeal membrane oxygenation (ECMO) became available in our institution in January 1991, ECMO was incorporated in a protocol of preoperative stabilization and delayed repair for congenital diaphragmatic hernia (CDH).[1] If ECMO was necessary for preoperative stabilization, surgical repair of the diaphragmatic defect was performed while the patient was on ECMO at the end of the ECMO-run.[2]

In the early experiences with this approach significant postoperative bleeding complications were encountered at the surgical site.[2] In all first six patients – who form part of this study – bleeding complications occurred, requiring 455 to 1215 mL red blood cells (RBC; mean 850 mL). Four of the 6 patients were forcefully weaned from ECMO because of the hemorrhage, and three of these four died of recurrent pulmonary hypertension.

Wilson et al. were the first who described the effect of an antifibrinolytic agent on hemorrhagic complications during ECMO.[3] They administered ϵ-aminocaproic acid (EACA) to 42 patients who were considered to be at high risk for bleeding complications (such as anticipated surgical procedures, preexisting intracranial hemorrhage [ICH] or profound hypoxia), starting just before or after cannulation until decannulation. Compared with 68 patients not receiving EACA, the patients who received EACA had significantly less bleeding while on ECMO and required fewer blood transfusions. This difference was most significant in the congenital diaphragmatic hernia and cardiac subgroups. The incidence of ICH in the neonatal subgroup was also significantly reduced in the EACA group. These investigators advocated the use of EACA for all patients who were thought to be at risk for hemorrhagic complications on ECMO.

Therefore we adopted the use of an antifibrinolytic agent as advocated by Wilson et al.[3] Since January 1993 we administered tranexamic acid (TEA) during and after CDH repair on ECMO. In this report our experience with hemorrhagic and thrombotic complications in CDH repair during ECMO is presented, and the effect of TEA is evaluated.

Materials and Methods

Since January 1991, 20 high-risk CDH patients needed ECMO support for preoperative stabilization in our institution. In all patients veno-arterial ECMO was used as described by Bartlett et al.[4] During the ECMO run heparin was titrated to maintain the activated clotting time (ACT) at levels of 200 to 220 seconds with ECMO flow rates higher than 250 mL/min.

ACTs were monitored at the bedside using the Hemochron (International Technidyne Corporation, Edison, NJ). At lower ECMO flow rates higher ACT levels were maintained (for example ACT levels of 240 to 250 seconds at ECMO flows of 50 to 200 mL/min). ACT goals were not different in any one of the groups. Thrombocytes were administered to maintain their count above the level of 80 x 10^9/L pre-CDH repair and above 100 x 10^9/L during and after CDH repair. The ACT was monitored every hour, and the platelet counts were determined every 8 hours. RBC's were routinely transfused to maintain the hematocrit greater than 40% and the hemoglobin-concentration above 8.0 mmol/L. CDH repair was performed at the end of the ECMO run if the patient was weanable from ECMO and the ECMO flow could be decreased to 50 mL/min.

During surgery we avoided major dissections and incidental procedures, and we used running sutures to close the defect. If the defect was too large for primary closure a prosthetic patch (Gore-tex soft tissue patch) was used. Fibrin-glue was spred on the suture line at the end of the repair. During and directly after surgical repair we tried to preclude major bleeding complications by running high ECMO flows, which allow relatively low ACTs (aim, 180 to 200 seconds). This strategy was the same during the whole study period. The surgical procedure has been founded on a long-lasting experience, did not undergo a fundamental change and was performed by the most experienced surgeon in the first group and by several surgeons in the second group.

Nineteen patients underwent elective repair while on ECMO; in one patient ECMO was stopped because of a severe intracranial hemorrhage at day 1 of ECMO, and she died.

The patients were divided into 2 groups. Group 1 consisted of 9 patients who underwent repair without the use of TEA (1991 to 1992) and group 2 contained 10 patients who received TEA (1993 to 1995).

Except for the addition of TEA the ECMO-protocol was identical for both groups.

TEA administration happened in different ways. In the first patient TEA was given intermittently by intravenous infusion, 15 mg/kg every 8 hours, during the first 48 postoperative hours. In all other patients TEA was administered by an intravenous loading bolus just before surgery (10 mg/kg in patients 2 and 3, and 4 mg/kg in the ensuing patients), followed by a continuous intravenous infusion of 2 mg/kg/h TEA over 48 hours in the second patient and of 1 mg/kg/h TEA over 24 hours in the third and ensuing patients.

For all patients the total blood loss was recorded. Total blood loss was defined as the peroperative blood loss from the surgical site and the postoperative bleeding from the chest tube. The blood losses were calculated in reference to the body weight and the postoperatieve ECMO time (ie milliliters blood per kg body weight and per postoperative ECMO hour). The

transfusion requirements of red blood cells were assessed for the whole ECMO run as well as in relation to the weight of the patients, the duration of the ECMO run and the moment of CDH repair. The incidence of reexploration for bleeding and the thrombotic complications were noted in addition to the incidence of forced discontinuation of ECMO because of bleeding.

For statistical analysis of the differences in both groups the two-sided Wilcoxon's rank sum test and the two-sided Fisher's Exact test were used. P values of less than 0 05 were considered significant.

Results

Both groups were comparable with respect to birthweight, age at institution of ECMO, side of the defect, patch repair, and the time of CDH repair during ECMO (Table 1) Only for the duration of the ECMO run there was a significant difference between both groups Seven of the nine group 1 patients (78%) and 9 of the 10 group 2 patients (90%) had a left-sided defect. Patch repair was accomplished in 16 patients 8 of group 1 (89%) and 8 of group 2 (80%).

Table 1 **Demographic data**

	group 1 (n = 9)	group 2 (n = 10)	Wilcoxon p - value
birth-weight (g)	3200 (2880,3660)	3050 (2700,4050)	0.96
age at ECMO (h)	25 (18,27)	18 (16,28)	0.68
duration of ECMO (h)	181 (150,217)	130 (110,167)	0.02
time of CDH repair (ECMO h)	108 (87,143)	92 (67,110)	0 15

Note The median values are stated with the 25% and 75% percentiles for all variables

Hemorrhagic complications led to a forced discontinuation of ECMO support in five of the nine patients of group 1 – in one patient even after heparinization had been stopped. Four of the five patients who were removed earlier from ECMO because of bleeding died of rebound pulmonary hypertension. One patient in each group required an abdominal reexploration because of hemorrhage. There were four patients with thrombotic complications (two in each group). The thrombotic patient complications consisted of an upper caval vein thrombosis centered around a central venous line placed immediately after ECMO, at the time of decannulation, via the internal jugular vein. These complications seemed to be more severe in the first two patients of group 2. A chylothorax developed in both patients, which lasted for several weeks despite special MCT formulas and even complete discontinuation of enteral feeding. In one patient of group 1 the obstructed venous return may have led to a hydrocephalus. In addition, in two cases of group 2 there were clots in the circuit. The survival rate for group 2 (100%) was significantly higher than for group 1 (56%) (Fisher's Exact test, $p<0.05$).

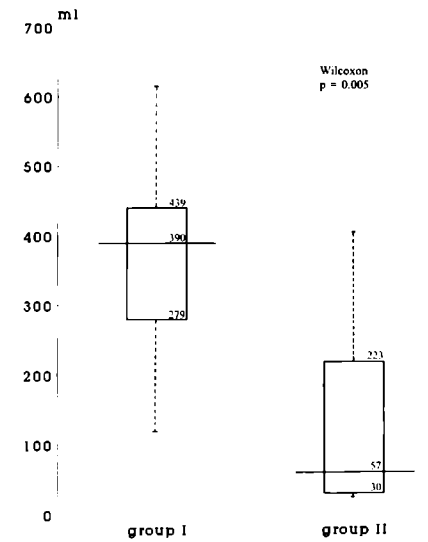


Figure 1a

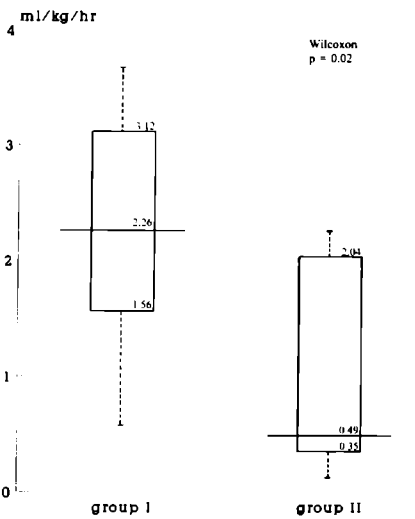


Figure 1b

Figure 1 Box-plots of intra- and postoperative blood loss after CDH repair on ECMO in both groups (group I without the use of TEA, group II with TEA). They illustrate the distribution of data. The bottom and the top of the box indicate the first and third quartile, the line in between indicates the median, and the dotted lines represent the extreme values (range). (a) total volume (mL) and (b) volume per kg body weight per postoperative ECMO time (mL/kg/h)

The median total intra- and postoperative blood loss was significantly different: 390 mL in group 1 versus 57 mL in group 2 (Wilcoxon's rank sum, p = 0.005; Fig 1a). The median intra- and postoperative blood loss in reference to the postoperative ECMO time and the body weight was significantly less in group 2: 2.26 mL/kg/h in group 1 versus 0.49 mL/kg/hr in group 2 (Wilcoxon's rank sum, p = 0.02; Fig. 1b).The median transfusion requirement of RBC during an ECMO run in group 1 was significantly more than in group 2: 838 mL versus 442 mL (Wilcoxon's rank sum, p = 0.003; Fig. 2a). In respect to the preoperative transfusion requirement of RBC there is no difference between both groups: median amount of 0.83 mL/kg/h (group 1) versus 0.96 mL/kg/h (group 2; Wilcoxon's rank sum, p = 0.3). The difference in intra- and postoperative requirements of RBC between both groups is statistically significant: median of 2.96 mL/kg/h in group 1 versus 1.13 mL/kg/h in group 2 (Wilcoxon's rank sum, p = 0.03; Fig. 2b).

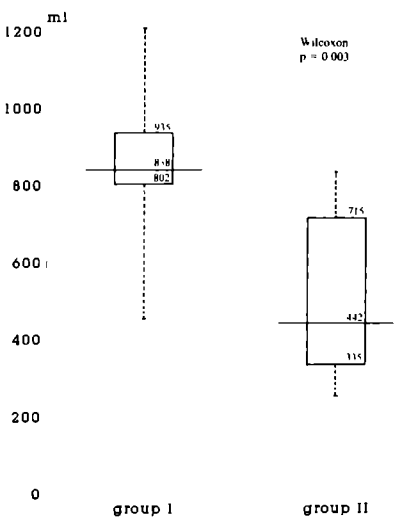


Figure 2a

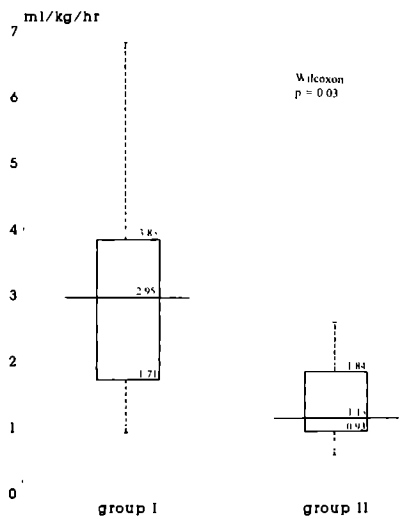


Figure 2b

Figure 2 Box-plots of transfusion requirements of RBCs in CDH patients, treated without (group I) and with TEA (group II). They illustrate the distribution of data. The bottom and the top of the box indicate the first and third quartile, the line in between indicates the median and the dotted lines represent the extreme values (range). (a) total volume during the whole ECMO run. (b) volume per kg bodyweight per postoperative ECMO hour (mL/kg/h)

Discussion

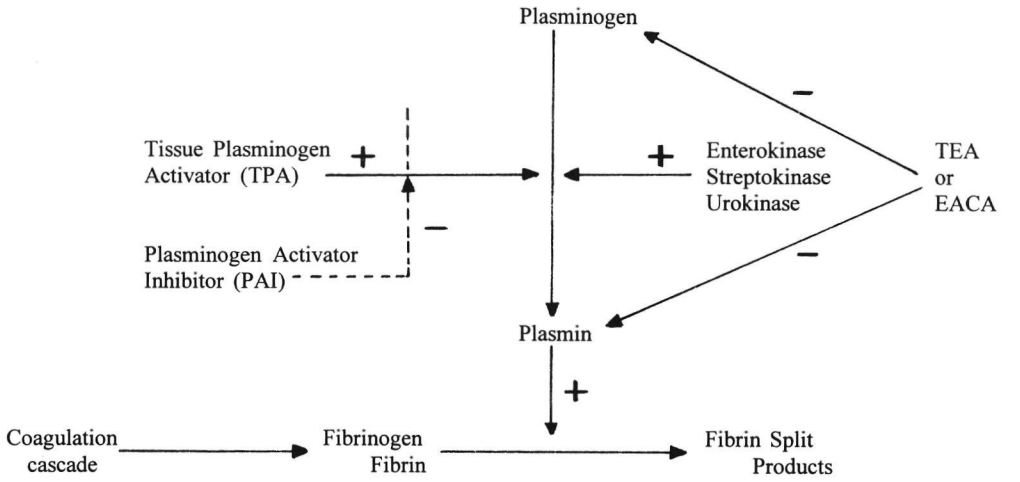
Hemorrhage is the major complication in neonates during ECMO. Among all Extracorporeal Life Support Organization (ELSO) registry patients treated by ECMO hemorrhagic complications occurred in 21%[5]. In CDH patients treated by ECMO the overall incidence of bleeding complications appears to be 43% (209 of 483) including a 24% (117 of 483) incidence of operative site bleeding[6]. Repair of the hernia defect while on ECMO may increase the risk of bleeding complications up to 58 to 60%[6,7]. Our initial experience – reflected in group 1 of this study – is consistent with these reported rates: six of the first 10 CDH patients treated by ECMO had severe hemorrhage (intracranial 1; surgical site 5).

Hemorrhagic complications are a hallmark of poor outcome[7]. A statistically significant difference in bleeding complications has been found between surviving and nonsurviving CDH patients who needed ECMO support[6,7]. The reported incidence of fatal hemorrhage is 4% to 5%[6,8]. However, this rate is probably higher because any hemorrhagic complication may force the patient to be removed from ECMO earlier, and the immediate cause of death would be classified as pulmonary failure rather than hemorrhagic[6]. We only can confirm this experience because all patients who died in this series had major hemorrhagic complications. So far we repair CDH on ECMO late in the ECMO course when the patient had been shown to be weanable from ECMO. In this concept, a recurrence of persistent pulmonary hypertension of the newborn (PPHN), elicited by the surgical procedure and the consequently diminished thoracic compliance, can be controlled by ECMO, whereas ECMO could be withdrawn soon in case of hemorrhagic complications.

Adhering to our strategy, in which the benefits of perioperative ECMO support have to be outweighed by the risks of hemorrhagic complications, it seemed to be important to diminish the chance of those complications. Initially it was thought that bleeding complications during ECMO were caused by the anticoagulation. Undoubtedly heparinization is an important, but certainly not the only, factor for the occurrence of hemorrhage. It is known from the cardiopulmonary bypass (CPB) surgery, that fibrinolysis is a cause of postoperative bleeding and that the fibrinolytic activity increased immediately after CPB had begun and remained elevated throughout the period of extracorporeal circulation (ECC)[9]. So, the increased fibrinolytic activity seems to be caused by ECC itself[9]. Fibrinolysis is believed to play a role in the increased hemorrhagic tendency in patients who require extracorporeal life support (ECLS) as well[10,11].

The increased fibrinolysis during ECC and ECLS is possibly caused by an imbalance between tissue plasminogen activator (TPA) and plasminogen activator inhibitor (PAI), two of

the major components regulating fibrinolysis (Fig 3)[11]. McVeen et al found a marked elevation of both PAI activity and TPA antigen in pre-ECMO infants experiencing respiratory distress[10].



Epsilonaminocaproic Acid (EACA) and tranexamic acid (TEA) inhibit fibrinolysis by binding to plasminogen and plasmin. Urokinase and TPA accelerate the formation of plasmin from plasminogen.

Figure 3 Schematic diagram of the fibrinolytic system

After institution of ECLS there is a rapid reduction of PAI activity within 24 hours, whereas TPA levels appear to remain more elevated and decline more gradually during ECMO treatment[10]. This imbalance may cause an increased risk for hemorrhage. Therefore, antifibrinolytic therapy represents a pharmacological modality to reduce hemorrhagic complications on ECMO.

Drugs used to inhibit fibrinolysis during and after CPB surgery are epsilon-aminocaproic acid (EACA), tranexamic acid (TEA) and aprotinine[12,13]. EACA and TEA inhibit fibrinolysis by binding to the lysine binding sites of plasminogen and plasmin, which are the binding sites for fibrin. In this manner they blocked the fibrin breakdown by plasmin. The affinity of TEA for plasminogen is much stronger than EACA, so that TEA is 6 to 10 times as potent as EACA[13]. Moreover TEA also competitively inhibits the activation of enterokinase. EACA has

been adopted for use in neonatal ECLS patients by Wilson et al[3] Because EACA was not registered in the Netherlands, we choose TEA instead of EACA Because the optimal dosage of TEA for neonates on ECMO is not known, we tried to determine the dosage and the means of administration on the basis of the report of Horrow et al about TEA[13] The recommended dosage by the manufacturer and the dosage of EACA used by Wilson (taking into consideration the greater efficacy of TEA) gave us guidelines for the dosing scheme [3,13]

Patients who received TEA perioperatively had significantly less blood loss while on ECMO than the patients who did not receive TEA (Wilcoxon's rank sum, p = 0 005) Similarly the transfusion requirements of RBC were significantly less in the TEA-treated group (Wilcoxon's rank sum, p = 0 003) No patients in the TEA-treated group had to be withdrawn early from ECMO support because of major bleeding The survival rate for group 2 was much higher (100% vs 56%) The improved survival in group 2 may be attributed to the decreased occurrence of severe hemorrhages

Those data may reflect the possibility that antifibrinolytic therapy has played a role in the diminution of bleeding complications and the improved survival However, these results may be attributed as well to the increased experience of the whole ECMO team

Because this is an unblinded study with historical controls, it is more difficult to unravel the influence of the gained experience on the one hand and the influence of TEA on the other hand on the improved results It can be supposed that less blood loss and less RBC requirement can be explained by a better and more well-balanced anticoagulation management in the second group as a result of learning over time

To investigate the effect of the learning curve, the RBC requirements were studied in all other ECMO patients (CDH excepted) in the same time frames as group 1 and 2 CDH patients were treated In the first episode (1991 to 1992) the median RBC requirement during ECMO was 0 66 mL/kg/h of ECMO versus 0 75 mL/kg/h in the second episode (1993 to 1995, p=0 27) This observation does not suggest a big alteration in ECMO handling caused by the learning curve

With respect to the operative technique there was no fundamental change in the surgical approach with the advent of ECMO This technique has been rooted in a more than 20-year surgical experience with CDH repair So it is hard to believe that a learning curve or a big alteration in the operative procedure is responsible for the bleeding complications in the early part of this study (Group 1 CDH patients)

Although the validity of this study may be a point of debate because of the use of historical controls, the following points can be made

(1) The preoperative RBC requirements in CDH-patiens on ECMO in both episodes

(0.83 mL/kg/h in group 1 and 0.96 mL/kg/h in group 2) were comparable to the RBC requirements in all other indications in both episodes (0.66 mL/kg/h and 0 75 mL/kg/h respectively).

(2) The postoperative RBC requirements after CDH repair on ECMO in the second episode (group 2, 1 13 mL/kg/h) were comparable to the RBC requirements in the pre-CDH repair episodes (0 83 to 0 96 mL/kg/h) and in all other ECMO indications (0.66 to 0.75 mL/kg/h).

(3) The postoperative RBC requirements after CDH repair on ECMO in the first period (group 1 without the use of TEA, 2.96 mL/kg/h) differed significantly from the requirements in the second period (group 2 with the use of TEA, 1.13 mL/kg/h, p=0.03).

(4) The surgical procedure was well established over years and did not change with the introduction of ECMO or during the study period

Therefore it may be concluded that TEA is effective in controlling bleeding complications and in reducing RBC transfusion requirements.

Although thrombotic complications are to be expected by the use of TEA, the reports concerning antifibrinolytic therapy during and after CPB surgery did not show an increase in those complications[12,13]. In this study rather severe thrombotic complications were encountered in the first two patients treated with TEA. Right atrial and superior caval vein (SCV) thrombosis developed with an SCV syndrome and a long-lasting chylothorax. It was unclear whether these complications of central venous line thrombosis several days after ECMO were caused by TEA because we experienced the similar complications previously in two patients of group 1 who did not receive TEA. In addition those complications have been reported as well after ECMO without the use of antifibrinolytic therapy[14,15], and thrombosis around an indwelling central venous line is a fairly known complication in neonates[16]. However, meeting these problems and noting fatal thrombotic complications by the use of antifibrinolytic therapy[17], we decided to adapt the dosage and the administration of TEA. Since that alteration, neither severe hemorrhages nor severe thrombotic complications were observed.

This study demonstrates that TEA is effective in reducing postoperative blood loss and hemorrhagic complications associated with CDH repair on ECMO. It also reflects the possibility that TEA may be responsible for severe thrombotic complications. Empirically, based on our experience, the appropriate dosage and administration pattern of TEA for CDH repair during ECMO seem to be one bolus of 4 mg/kg TEA intravenously 30 minutes before the anticipated CDH repair and a continuous infusion of 1 mg/kg/h TEA during 24 hours after CDH repair.

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Chapter 9

Surgical Repair of an Aortic Coarctation in a patient after treatment with Extracorporeal Membrane Oxygenation

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Abstract

Extracorporeal membrane oxygenation (ECMO) is a lifesaving treatment for neonates who have severe respiratory failure that does not respond to maximal conventional therapy. A consequence of venoarterial ECMO is the sacrifice of the right common carotid artery. Evaluation of the impact of a single carotid artery in babies treated with ECMO concerns mostly long-term neurodevelopmental outcome. The authors encountered a peculiar problem caused by a single carotid artery in a post-ECMO patient during the surgical correction of aortic coarctation with hypoplastic distal aortic arch. For patients with a confirmed cardiac malformation that necessitates future surgical repair and for whom ECMO support is required, reconstruction of the right common carotid artery should be considered. Venovenous ECMO is an alternative solution if this approach is not contraindicated because of the patient's clinical condition. Patients with congenital diaphragmatic hernia have a higher incidence of cardiac malformations; therefore, careful cardiological attention is required. Anomalies masked by pulmonary hypertension also must be considered.

Introduction

The treatment of congenital diaphragmatic hernia (CDH) in neonates has received new perspectives by the application of extracorporeal membrane oxygenation (ECMO)[1]. With venoarterial ECMO, cannulation and ligation of the right common carotid artery are inevitable. In many ECMO centers, efforts are made to save the carotid artery either by its reconstruction after ECMO or through avoiding arterial cannulation and initiating venovenous (VV) access if possible The early complications and late sequelae of a single carotid artery are studied intensively in most ECMO centers, however, these studies are focused primarily on cerebral circulation and long-term neurodevelopmental outcome[2,3].

We report on a baby with CDH treated with venoarterial ECMO. The patient's clinical course was complicated by the development of an aortic coarctation, diagnosed after decannulation. Surgical correction of the associated hypoplastic distal aortic arch was incomplete because of the ligated right common carotid artery and the impossibility of clamping the remaining left carotid artery

Case report

A 3.500-g white boy was born by spontaneous vaginal delivery after 40 weeks of uneventful gestation. The neonate had severe respiratory distress and was transferred to our clinic. The Apgar scores were 4 and 6 at 1 and 5 minutes, respectively. A chest radiograph showed a left-sided diaphragmatic hernia. Intensive artificial ventilation and pharmacological support with vasoactive drugs did not result in satisfactory gas exchange. The initial cardiac evaluation showed a wide patent ductus arteriosus with a bidirectional flow, but no structural anomalies were evident (Fig 1).

ECMO via venoarterial access was initiated. Six days later, surgical repair of the diaphragmatic defect was performed while the patient was on ECMO. The postoperative course was complicated by hemorrhages at the surgical site, hypotension, poor diuresis, distension of the abdomen, and poor venous return to the extracorporeal circuit. An increase in fluid intake, transfusions of blood products, pharmacological support with vasoactive drugs, and surgical decompression of the abdomen, widened by a Goretex patch (W.L. Gore and Associates, Inc, Flagstaff, AZ), did not result in improved circulation Subsequently, as the parameters of gas exchange became satisfactory, the patient was weaned from ECMO. After decannulation, the hypotension continued to persist. Total anuria developed, and gas exchange worsened. Echographic examination of the abdomen showed an empty bladder, without compression of

the kidneys or the inferior caval vein. Echocardiographic examination showed a paraductal aortic coarctation and a small patent ductus arteriosus with a bidirectional shunt (Fig 2).

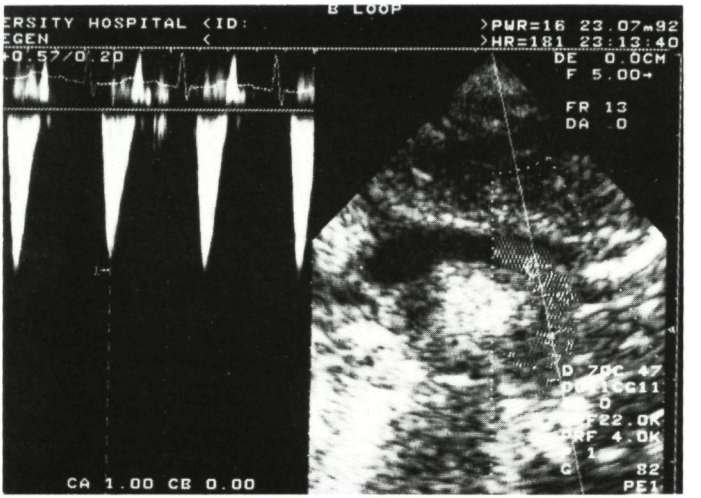

Fig 1 Echocardiographic image of the aorta before iniation of ECMO

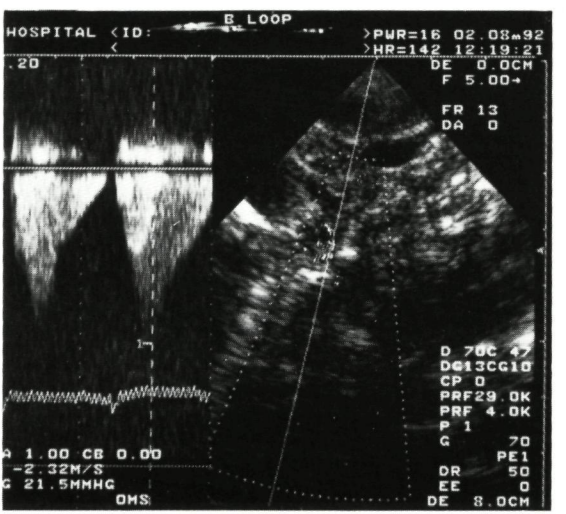

Fig 2 Echocardiographic image of the aorta after decannulation

Prostaglandin therapy resulted in rapid improvement of the patient's clinical condition. Four days later, extended resection of the isthmic coarctation was performed, followed by end-to-end anastomosis at the inferior side of the aortic arch. The ductus arteriosus was closed; however, a more proximal anastomosis on the proximal aortic arch was not possible because the single left carotid artery could not be clamped. An evaluation performed immediately after the surgery showed a residual gradient of approximately 20 mm Hg between the right upper extremity and the umbilical artery.

The patient was extubated 21 days after decannulation, and 17 days later was transferred to the referring hospital. Cardiological examinations performed 2 months and 1 year later did not show residual or recurrent aortic arch stenosis (Fig 3). The patient's current clinical condition is satisfactory, but his psychomotor development is retarded because of cerebral atrophy and ventriculomegaly, probably caused by asphyxia and cerebral anoxia before ECMO was begun.

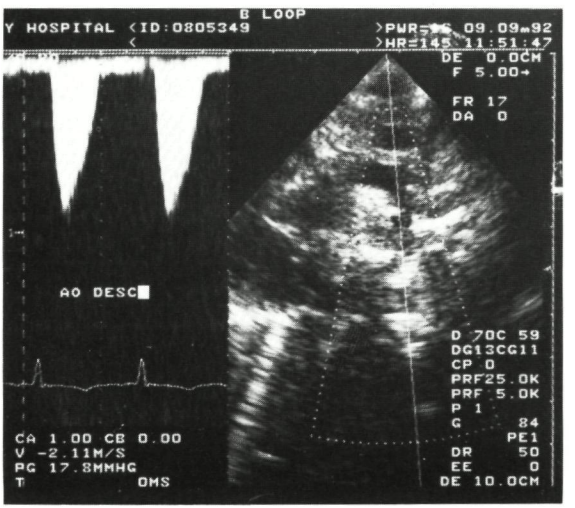

Fig 3 Echocardiographic image of the aorta after repair of the coarctation and the hypoplastic distal aortic arch

Discussion

Despite the growing importance of ECMO in the treatment of CDH and other severe neonatal respiratory failure, well-documented reports proving the deleterious consequences of the cannulation and ligation of the great vessels in the neck are still scarce. The possibility of sudden cerebral ischemia caused by an anomalous circle of Willis, which results in insufficient blood supply to the right hemisphere at the moment of cannulation of the right carotid artery, has been a concern[4]. Most studies of late complications of ECMO concern the possibility of sequelae related to psychomotor development[5]

We encountered a technical difficulty, which arose a few days after decannulation, during the surgical repair of an aortic coarctation with hypoplastic distal aortic arch, and was related to the absence of the second carotid artery. Similarly, as a late sequela of venoarterial ECMO, the same technical problem theoretically can occur during the surgical repair of traumatic injuries of the left carotid artery In cases of advanced atherosclerosis, the collateral vessels are believed to be sufficient for ensuring adequate blood supply to the brain.

Before ECMO, only a patent ductus arteriosus, without coarctation, was demonstrated in our patient Closure of the ductus arteriosus led to paraductal coarctation because of fibrotic changes and traction on the aortic wall; this was confirmed by the presence of a fibrotic ring at the site of the opening of the ductus into the aorta, and this ring is frequently associated with a hypoplastic distal aortic arch.

Awareness of the presence of any cardiac malformation in CDH patients is essential before initiating ECMO. The possibility that anomalies can become evident through functional circulatory changes in the course of pulmonary hypertension during an ECMO procedure must be considered.

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Chapter 10

Recurrent Congenital Diaphragmatic Hernia; which factors are involved?

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Eur J Pediatr Surg 7:1997 (in press)

Abstract

After successful ECMO treatment for CDH patients recurrent hernia was noted more frequently. This observation gave rise to a retrospective study in which we attempted to identify risk factors for a recurrence. The medical records of 66 surviving children born with congenital diaphragmatic hernia were reviewed. Fifty-seven patients had a left sided defect and 9 paitents a right sided defect. The diaphragmatic defect was repaired by primary suture in 54 patients and by a prosthetic patch closure in 12 patients. Conventional mechanical ventilation with pharmacological support sufficed in 55 patients, whereas 11 patients required ECMO support The defects were divided into 3 groups according to the dimensions of the defect (small, moderate or large) Nine patients (14%) developed a recurrent hernia on the average of 4.0 months (range 0 2 - 6 9) after the initial repair Recurrences occurred (1) in 5 patients with a left sided defect (9%) and in 4 patients with a right sided defect (44%), (2) in 4 patients with a primary repair (7%) and in 5 patients with a prosthetic patch repair (42%), (3) in 5 patients who were treated conventionally (9%) and in 4 patients who required ECMO support (36%) and (4) in 5 patients with a small or moderate defect (8%) and in all 4 patients with a large defect (100%). In conclusion, large patch-repaired right sided defects in patients who required ECMO stabilization are risk factors for the development of a recurrent hernia.

Introduction

Congenital diaphragmatic hernia (CDH) is one of the unsolved problems in paediatric surgery. Despite all kinds of innovations, including extracorporeal membrane oxygenation (ECMO) the mortality is still high Besides the complicated pathophysiology there are still surgical problems, especially in children with large defects Little is known about the ideal reconstruction of large defects, the best prosthetic material for patching, the fate of prosthetic patches, the late sequelae of large defects and the risk factors for a recurrence of a hernia This study evaluates which factors are involved in the recurrences

Patients and methods

From 1980 to 1994 116 neonates with a congenital posterolateral diaphragmatic defect were referred to the Department of Paediatric Surgery of the University Hospital of Nijmegen The charts of these infants were reviewed retrospectively Forty-five patients died in the neonatal period. Since January 1991 ECMO has been used for severely affected neonates Seventy-one patients (61%) survived the initial treatment 60 patients, who were treated conventionally and 11 patients who received ECMO support. Two survivors of these 71 patients were mentally retardated and died of pneumonia at the age of 5 and 11 months respectively and 3 patients were lost to follow up, leaving 66 patients for this study. Data collected included demographics, side and dimensions of the primary defect, presence of a hernial sac, the technique used to close the defect (e.g. primary suture or patch repair), the condition during follow up visits, the incidence of a recurrence and the time between the surgical correction and the recurrence. In general the diaphragmatic defect was repaired by primary closure using interrupted non-absorbable sutures. In those cases, in which primary closure was impossible a prosthetic patch was used (Lyo-dura n = 3 and Gore-Tex n = 9). The repair was accomplished through a transabdominal approach in all patients except one

Patients were divided in three groups according to the dimensions of the defect small (less than 1/4 absence of hemidiaphragm), middle (1/4 to 3/4 absence) and large (more than 3/4 absence).
A chest x-ray was made routinely at the age of 3 and 12 months and at other times if necessary. A recurrent hernia was diagnosed by chest x-ray and / or upper gastrointestinal contrast study.

The clinical features between the successfully repaired group and the group with a recurrent hernia were compared using the Fisher's Exact test or the Wilcoxon two sample test. A p value of <.05 was considered statistically significant. To investigate the possible confounding of different factors logistic regression analyses were applied. The relation between recurrence of the hernia and the separate factors can be expressed with the oddsratio. An oddsratio of less than 1 means that the absence of the factor involved gives a higher risk for recurrence. An oddsratio of more than 1 means that the presence of the factor gives a higher risk for recurrence. The statistical analyses were performed using the statistical software package SAS^R, version 6, Sas Institute Inc.

Results

Fifty-seven of the 66 studied children (86%) had a left sided hernia (Table 1). Eleven patients received ECMO perioperatively. Twelve (18%) had defects which were too large for primary closure and required a prosthetic patch. Nine patients developed a recurrent hernia at an average of 4.0 months (range 0.2 - 6.9) following initial surgical repair. Except for one patient, in whom the recurrence was found on a routine chest x-ray, all patients with a recurrence presented with dyspnoea (n = 5) and / or feeding problems (n = 6). All but one recurrences were reoperated. Six recurrent defects were closed primarily and in one patient a patch was used. In one other patient a second patch was placed. Two patients developed a second recurrent hernia.

There were no statistical differences between the successfully repaired group and the group of recurrent hernia concerning gender, gestational age and birth weight (Table 1). Statistically significant differences between the successfully repaired group and the group with a recurrent hernia were found for right sided defects, ECMO treatment, the necessity of using a patch and the size of the defect.

The distribution of the patients by size of the defect, side of the defect, type of surgical repair, ECMO treatment and the incidence of a recurrent hernia are listed in Table 2.

Table 1 **Clinical features of neonates with CDH after successful repair and recurrent hernia**

	Total repair (n=66)	Successful repair (n=57)	Recurrent hernia (n=9)	P Value
Gender				NS*
Male	37	32	5	
Female	29	25	4	
Gestational age (wk)[1]	39.1 ± 2.5	39.1 ± 2.5	39.1 ± 2.4	NS**
Birth weight (kg)[1]	3.1 ± 0.7	3.1 ± 0.7	3.0 ± 0.7	NS**
Location defect				<.05*
left	57	52	5	
right	9	5	4	
Treatment				<.05*
conventional	55	50	5	
ECMO	11	7	4	
Technique to close the defect				<.01*
primary	54	50	4	
patch	12	7	5	
Dimensions defect				<.001*
small	17	16	1	
middle	45	41	4	
large	4	0	4	
Presence of hernial sac				NS*
no	50	42	8	
yes	16	15	1	

[1] Mean ± SD Abbreviation: NS, not significant

* Fisher's Exact test, ** Wilcoxon two sample test

Table 2 **Distribution of patients by size of the defect, location, surgical repair, ECMO treatment and the incidence of a recurrent hernia**

		left sided				right sided			
		primary		patch		primary		patch	
size	number	CT	ECMO	CT	ECMO	CT	ECMO	CT	ECMO
small	17 (1)	16	0	0	0	1 (1)	0	0	0
middle	45 (4)	30 (1)	1	1	6 (1)	5 (2)	1	1	0
large	4 (4)	0	1	1 (1)	2 (2)	0	0	0	1 (1)
total	66 (9)	46 (1)	1	2 (1)	8 (3)	6 (3)	1	1	1 (1)

Note: number of recurrent hernias between brackets, CT = conventional treatment

Logistic regression analyses were performed for the whole group and after removal of the 4 patients with large defects to find possible predisposing factors for the relapse of a hernia. These 4 patients were omitted because they all had recurrences and therefore strongly influence the results concerning the variables correlated with the size of the defect. The oddsratios showed that the right sided defects, the use of a patch and in lesser extent the ECMO treatment are the main factors for a relapse of a hernia (Table 3a and 3b).
A strong correlation was found between the use of a patch and the size of the defect, as could be expected by the conducted management strategy. A hernial sac was found in 16 patients (24%) during their first operation. The finding of a hernial sac during the initial operation appears to lower the risk for a relapse of a hernia.

Discussion

A recurrent hernia is one of the complications following successful initial treatment for congenital diaphragmatic hernia. In the literature there are only a few communications concerning rehernіation before 1990, suggesting that rehernіation was not a major problem in those days. However, it is very likely that this problem was secondary to the issue of survival for CDH. Nevertheless, in 1981 Cohen and Reid described 13 recurrences among 58 survivors (22% recurrence rate).[4] Because of the limited attention paid to this subject little is known about the incidence and the risk factors for the occurrence of a rehernіation.

We found 9 relapses in 66 reviewed CDH survivors (14% recurrence rate). This overall recurrence rate seems not to differ unfavourably compared to the recurrence rates reported in literature (Table 4). In this study significant differences between the "successful group" and the "recurrence group" were found for the following variables: 1) the presence of a right sided diaphragmatic defect (44% recurrence rate); 2) ECMO treatment (36% recurrence rate); 3) the dimensions of the defect; 4) and the unfeasibility for primary closure of the diaphragmatic defect (42% recurrence rate, Table 1).

Table 3 **Oddsratios (OR) for a recurrent hernia**

Table 3a **Oddsratios and corrected oddsratios for patch (ORp), location and of the defect (ORl)**

	OR	ORp				ORl		
Patch	8.9*	12.8*	8.0	8.1*	8.6*			
Location¶	8.3*	12.7*				9.5*	7.5*	10.6*
ECMO	5.7*		1.2			6.6*		
Size#	3.1			1.4			2.4	
Hernial sac	0.4				0.4			0.2

Table 3b **Oddsratios and corrected oddsratios for location of the defect (ORl) for patients with small and middle size defects**

	OR	ORl			
Location¶	15.6*	16.1*	16.1*	15.7*	18.1*
Patch	1.8	2.1			
ECMO	1.8		2.1		
Size§	1.6			0.9	
Hernial sac	0.7				0.4

An oddsratio of > 1 is considered as an increased risk for rehernıation

*P< 0.05 ¶Right versus left #Large and middle versus small §Middle versus small

Table 4 **Recurrences of CDH, reported in literature linked up with conventional treatment (CT) and or ECMO-treatment and in respect of the way of closing the diaphragmatic defect (direct suture, patch or muscle plasty)**

authors	numbers of survivors	overall recurrence rate	kind of therapy	recurrence rate	direct suture	recurrence rate	kind of prosthetic material	recurrence rate
Cohen/Reid (1981)[4]	58	22%	CT	22%	58	22%		
Bax/Collins (1984)[3]	8	13%	CT	13%			8 *	13%
Koot (1993)[7]	40	13%	CT	13%	16	0	24 ¶	21%
Wischermann (1995)[18]	45	4%	CT	4%	NT		NT	
Ehren (1992)[5]	52	12%	CT/ECMO#	12%	NT		NT	
Atkinson (1992)[2]	5	80%	ECMO	80%			5 §	80%
Lally (1992)[9]	18	50%	ECMO	50%	NT		NT	
v Meurs (1993)[16]	18	22%	ECMO	22%	14	14%	4 ∩	50%
West (1992)[17]	58	15%	CT (43)	9%	NT		NT	
			ECMO (15)	33%	NT		NT	
this study (1996)	66	14%	CT (55)	9%	52	8%	3 ¶	33%
			ECMO (11)	36%	2	0	9 §	44%

not split up NT= not traceable, which kind of repair was used and/or how many times with which results

* Teflon, Prolene, Marlex and Lyodura; ¶ Lyodura; § Gore-tex; ∩ not mentioned which kind of prosthetic material

These variables are not independent factors in the relapses of CDH although the oddsratios indicate that the right sided location, the size of the defect and / or use of a patch and in lesser extent the ECMO treatment are the main factors in the development of a recurrent hernia (Table 3a and 3b).

We have no explanation for the higher incidence of recurrences at the right side, just as the reason for the increased mortality in right sided defects has not yet been elucidated. These defects constitute probably a distinct entity different from the left sided hernias Perhaps the impaired visual field due to the position of the liver makes it more difficult to close the defect. A transthoracic approach to right sided defects may enable a better view and contribute to a more satisfying closure of the hernia.[6 18]

The increased incidence of relapses following ECMO treatment has been reported also by other authors. ranging from 22% to 80% (Table 4) Therefore it seems that ECMO is an important factor in the relapse of a hernia. Nevertheless ECMO, the size of the defect and the use of a patch are strongly correlated with each other. When we correct for the use of a patch by logistic regression analysis, it appears that the factor ECMO is less important in the development of a recurrence.

It is difficult to unravel the precise influence of each individual factor considering the strong coherence of the different factors and the limited numbers of patients.

In our institution CDH is repaired by direct suturing of the edges of the diaphragmatic defect. When the edges of the defect can not be approximated, the defect is regarded as being large and generally a prosthetic patch closure has been accomplished. Until the ECMO era the mortality among large-patch-repaired CDH patients was high with the exception of the series of Bax and Collins and presumably Koot et al. as well who used patch materials very generously to close the defect in order to create a diaphragmatic dome.[3 7] Since the use of ECMO the survival for CDH, especially in cases of large patch-repaired defects, has been improved (Table 5). It is obvious, that there is an increase of relapses concomitantly with the increased survival for patch-repaired CDH patients (Table 4). This is also emphasized by the fact that in our study 3 of the 4 recurrences in the ECMO treated group had large defects.

Table 5 **Survival for patch repaired-defects before and after the introduction of ECMO treatment**

	before ECMO era		ECMO era	
author	number of patch repair	number of survivors	number of patch repair	number of survivors
Atkinson (1991)[1]	6	0 (0%)	6	5 (83%)
West (1992)[17]	16	2 (13%)	13	11 (85%)
vd Staak (1996)[13]	14	2 (14%)	29	24 (83%)

It has been suggested, that recurrences depend on the kind of material used especially on the use of Lyodura.[7] However, recurrences were seen also after the use of Gore-Tex and other prosthetic materials.[2] Therefore it seems preferable to reconstruct the hemidiaphragm from living vascularized tissue if there is almost total agenesis of the hemidiaphragm so long as there is a minimal amount of native diaphragmatic tissue present for the attachment of a prosthetic patch.[11,12,16] However, an extensive dissection – e.g. for a reverse latissimus dorsi flap or an abdominal wall muscle flap – is a less feasible strategy, in cases where ECMO has been used, because of the potential risk of severe bleeding complications. Thus in that situation some type of prosthetic material has to be used.

As yet the question of which kind of foreign material should be employed for patching remains unanswered, not only in consideration of recurrences, but in view of the fate of the patch with growth as well.[3,8,14,15] At this moment it can be questioned, if Lyodura still is an option; there is doubt, whether Lyodura can transmit BSE.

Atkinson and Poon, who used Gore-Tex (expanded polytetrafluoroethylene), reported reoperations at 18 months of age and explained a rehernia tion by an impaired patch expansion.[2] In the present study recurrences were only noted before the age of 7 months, and not later on, indicating that an impaired incorporation of the patch in the first months is more a problem than the restricted size of the patch, which gradually becomes too small as the infants chest grows in the cross-sectional area. Probably, Touloukians observations, that persisting marginal skeletal muscle may reconstitute a portion of the diaphragmatic defect, might explain why recurrences seldom occur after a longer time (more than one year following the initial treatment).[14]

The risk of a relapse of a hernia seems to be lower when an hernial sac is found during the initial operation. The presence of a hernial sac was found in 24% of the patients during their first operation. Generally when this sac is not used for the closure of the defect it is excised to avoid its occupying space necessary for the lung. This sac could play a role in the recurrence because in four of nine patients a hernial sac was identified during the repair of their recurrent hernia. One can wonder whether this sac has been missed during the initial operation or develops later through a weak part in the reconstructed diaphragm.

In this study 3 recurrent hernias occurred in the group with middle size defects which were initially closed by primary suture. It can be questioned if the application of a patch in those defects causes less tension on the sutures and therefore results in less recurrences. Bax and Collins suggested that every defect should be closed by a patch in order to create a dome. In that way a dome would improve diaphragm function and keep the functional capacity small to avoid or lessen overstretching of the lungs.[3] However as pointed out above a recurrence probably develops because of lack of biological union between the patch and the diaphragm tissue and if so, the use of a patch should be minimized. Furthermore tension could contribute to the growth of persisting precursor tissue and therefore recreates a firm "new" diaphragm.[14] To get an answer to the question of which procedure is preferable for closing middle size defects and to gain a better insight into the development of biological union between prosthetic materials and diaphragm tissue and into the possible influence of tension on this union, experimental studies should be undertaken.

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Part V

Follow-up

Chapter 11

Congenital Diaphragmatic Hernia treated with Extracorporeal Membrane Oxygenation: outcome and early morbidity in the survivors

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Abstract

Purpose: Increasingly more children with CDH are surviving due to ECMO. Beyond the issue of survival arise the concerns of the morbidity, the outcome and the quality of life for these patients. The outcome and early morbidity of these survivors have been studied and compared with the outcome and early morbidity of CDH survivors who received conventional treatment in the same period (January 1991 through December 1996).

Methods. Twentythree survivors out of 29 ECMO treated CDH infants were enrolled in a routine ECMO evaluation program, whereas 15 of 17 survivors who recovered on conventional treatment (CT) could be followed retrospectively. The evaluation was divided into 4 parts: (1) medical and surgical complications, (2) respiratory condition, (3) growth and nutritional condition and (4) neurological and developmental outcome.

Results: Much more complications were noted in the ECMO group than in the CT group during the first admission. Chronic lung disease upon discharge and chronic respiratory illness at 1 year of age were encountered in respectively 61% and 60% of the ECMO survivors and in 20% and 36% of the CT survivors. The weight of many CDH survivors was below the 10th percentile: upon discharge and at one year of age respectively in 87% and 73% of the ECMO group and in 47% and 45% of the CT group. Nutritional disorders (such as need for tubefeeding, gastroesophageal reflux and swallowing problems) were noted in 57% of the ECMO survivors upon discharge and remained in 27% of them throughout the first year of life.

Neurological abnormalities at one year of age were met in 20% of the ECMO survivors and in 36% of the CT survivors. In the ECMO group the motor development was normal in only 33% of the children whereas the cognitive development was normal in 67% of the children. The average mental development score for the ECMO group fell within the normal range: 99 (range 55 to 125). The average motor development score fell more than one standard deviation below the norm: 0.73 (range 0.55 to 1.0). The delay in gross motor performance was chiefly related to respiratory restrictions which these infants still have at that age.

Conclusions: (1) the morbidity in high-risk CDH patients surviving due to ECMO is substantial and more than in these patients surviving with conventional treatment. However the outlook for these children remains encouraging with a reasonably low incidence of definite disabilities, and (2) taking into account the known mortality and the severe disability (impairment) at one year of age there is little doubt about the benefit of ECMO compared to conventional therapy for these high-risk CDH infants.

Introduction

Term or near-term newborns with a high likelihood of dying from reversible respiratory failure could be salvaged by extracorporeal membrane oxygenation (ECMO)[1,7]
This potentially lifesaving therapy is a highly invasive procedure with a temporary or permanent ligation of the right internal jugular vein and/or carotid artery and it requires systemic heparinization[2] This technique is applied in critically ill neonates, who suffer from hypoxia, acidosis, hypotension, hypo- or hypercarbia prior to ECMO therapy
All these conditions may affect cerebral blood flow and oxygenation and may cause central nervous system damage due to hemorrhage or infarction[3,8]
From the Extracorporeal Life Support Organization (ELSO) registry it is well known, that infants with CDH fare worst[9,10] CDH patients have longer ECMO runs, longer periods of mechanical ventilation and longer hospital stays than other ECMO-treated infants[10] In addition they require operative treatment, have a more unstable course and they have pulmonary hypoplasia The overall survival rate for ECMO treated CDH patients is only 59% which is lower than for other ECMO indications Even than this survival rate with ECMO therapy is better than with conventional treatment [11,13] In consequence there is concern, that improved survival with this technique might be offset by an increased risk of neurodevelopmental morbidity and long term disability
Therefore it is important to evaluate the outcome of ECMO treated CDH survivors This study describes the early morbidity and outcome in this population, compared with those of CDH survivors who received conventional treatment

Patients and methods

From January 1991 through December 1996 sixty patients with CDH who were antenatally diagnosed or who were symptomatic within 6 hours after birth, were referred to the Pediatric Surgical Center Nijmegen These patients were classified into the 3 categories as described below
"*Irretrievable' patients* These patients were (1) inborn neonates with severe respiratory distress, dying within 2 hours after birth before ECMO could be initiated, (2) newborns who died before or during transportation, (3) newborns with associated anomalies to whom not all therapeutic modalities were offered, or (4) newborns fulfilling ECMO entry criteria whose parents refused ECMO therapy They all died (n=12)

Conventionally treated patients These were newborns who recovered well on (maximal) conventional treatment (n=19). Seventeen of whom survived (89%). Fifteen of these survivors were followed retrospectively. Two were lost to follow-up; they were transferred to the referral hospitals while intubated and on the ventilator.
ECMO treated patients These were newborns who could not be stabilized by maximal conventional treatment and who received ECMO therapy (n=29). Twentythree of these patients survived (79%). These survivors were enrolled in a routine ECMO-evaluation program that was drawn up before the beginning of the ECMO program in our institution. In this preliminary study the outcome was evaluated upon discharge and at the age of 1 year. During the first year two late deaths were noted in the ECMO treated survivors. Nine patients have not yet reached the age of one year (4 conventionally treated and 5 ECMO-treated patients), whereas three patients were lost to follow-up (2 conventionally treated and 1 ECMO-treated). Thus 26 patients could be evaluated at the age of one year: 15 ECMO treated and 11 conventionally treated (CT) patients.

The evaluation has been divided into four parts:
1. Medical and surgical complications
2. Respiratory condition
3. Growth and nutritional condition
4 Neurological and developmental evaluation

Complications
Medical and surgical complications were listed, including all hospitalizations and surgical procedures.

Respiratory condition
The pulmonary condition was assigned as "normal", as "chronic lung disease" (CLD) if supplemental oxygen was required for more than 28 days after birth, and as "chronic reactive airway disease" (CRAD) if recurrent episodes with tachypnea and dyspnea associated with wheezing occurred for which bronchodilators and/or corticoids were necessary.

Growth and nutritional condition

At the fixed checkpoints weight and nutritional disorders were noted. By nutritional disorders or feeding problems we understand swallowing difficulties, food refusal and repetitive vomiting, the presence of gastroesophageal reflux and the need for tubefeeding The weights were plotted against age and compared to those of similar age groups and gender (percentile curve).

Neurological evaluation

In the ECMO group a routine screening was performed before discharge consisting of a physical examination by the pediatrician, a head ultrasonography (HUS), a cerebral computer tomography (CT), a brainstem auditory evoked response (BAER), an electroencephalography (EEG) and an ophthalmological consultation

At one year of age all children were examined by a pediatrician. Neurological abnormalities were defined as muscle tone abnormalities and abnormal tendon reflexes, chronic seizure disorder, blindness or deafness (interfering with normal function) Motor skills and cognitive or developmental skills were measured by a physical therapist and by a psychologist The Mental Developmental Index (MDI) from the Bayley scales of Infant Development and the Motor Quotient (MQ) according to Hoskins and Squires[14] were used for the developmental evaluation. The MQ was defined as the present motor age divided by the actual calendar age. The outcome was classified as "normal" if the score of a test was within one standard deviation (SD) of the test mean of the age group and no abnormalities were detected on physical/neurologic examination.A score of more than one but less than two SD's below the test mean were defined as "suspect" Outcome was assessed as "delayed", if the score was more than 2 SD's below the test mean or if neurologic abnormalities were identified.

Statistics

Because of the small number of patients only descriptive statistic are used

Results

Outcome upon discharge

The average hospital stay lasted for 80 days (range 42 to 177 days) in the ECMO group compared to 41 days (range 15 to 114 days) in the control group The longer hospitalizations were related to complications, chronic lung disease (CLD) and feeding problems The morbidity upon discharge for both groups is reported in table 1

Table 1 **Morbidity upon discharge**

	ECMO group (n=23)	CT group (n=15)
Complications		
patients with complications	15 (65%)	3 (20%)
number of complications	24	3
Respiratory		
CLD	14 (61%)	3 (20%)
CRAD	6 (26%)	3 (20%)
Oxygen at home	3 (13%)	0
Nutritional		
disorders	13 (57%)	6 (40%)
GER	9 (39%)	2 (13%)
Weight < P10	20 (87%)	7 (47%)
Neurological		
abnormal	2 (9%)	2 (13%)

Complications Twentyfour complications were observed in 15 patients of the ECMO group during the first admission (table 2) In the ECMO group 2 patients with a bowel obstruction received a temporary enterostomy after bowel resection because of intestinal ischemia In the CT group 3 complications were noted consisting of a chylothorax in 2 patients and a small bowel obstruction in 1 patient Large diaphragmatic defects which could not be closed by

primary suture were present in 20 patients (87%) of the ECMO group and in 5 patients (33%) of the CT group. CDH repair in these patients was accomplished with a polytetrafluoroethylene (PTFE-Goretex) patch. In 6 patients of the ECMO group the abdominal wall could not be closed by primary suture after CDH repair closure was accomplished with a PTFE patch. All 6 patients underwent reoperations for removal of the patch; in 4 of them because of septic complications.

Table 2 **Complications encountered in 23 ECMO CDH patients.**

Superior Vena Cava Syndrome	4
Chylothorax	2
Coarctatio Aortae	1
Hydrocephalus	1
Persistent PDA	2
Postoperative hemorrhage	5
Small bowel obstruction	4
Recurrent hernia	4
Abdominal wall patch	6

Note: More than one complication may be present in one patient

Respiratory condition In the ECMO group more respiratory problems were encountered than in the conventional group. Fourteen neonates (61%) of the ECMO group required supplemental oxygen for longer than 28 days (CLD) compared to 3 (20%) in the CT group. Nevertheless 17 ECMO survivors were able to leave the hospital without any kind of respiratory therapy.
Nutritional condition More feeding problems were encountered in ECMO CDH survivors than in the CT CDH survivors such as the need for tubefeeding and the need for antireflux medication. At the time of discharge in 87% of the ECMO CDH survivors the weight was below the 10th percentile (corrected for age and gender), whereas 47 % of the CT group survivors was below the 10th percentile.
Neurological status Two patients in each group had definite neurological abnormalities closely related to substantial (postanoxic) cortical atrophy. One of these patients in the ECMO group who was profoundly impaired died at the age of 11 months.

Outcome at one year of age

The morbidity at one year of age is summarized for both groups in table 3.

Table 3 **Morbidity at 1 year of age**

	ECMO-group (n = 15)	CT-group (n = 11)
Complications		
hydrocephalus	1 (7%)	0
recurrences	4 (27%)	0
small bowel obstruction	0	3 (27%)
Musculoskeletal		
chest wall deformity	8 (53%)	4 (36%)
scoliosis	1 (7%)	2 (18%)
Respiratory		
CRAD	9 (60%)	4 (36%)
oxygen at home	3 (20%)	0
Nutritional		
remaining on tubefeeding	4 (27%)	0
GER-medications	4 (27%)	3 (27%)
Growth		
weight below P10	11 (73%)	5 (45%)
median weight (gramms)	7650	9500
range	6900-10500	5500-11200
Neurological/developmental		
abnormal	2 (13%)	3 (27%)
hearing loss	1 (7%)	1 (9%)

Complications In the first year of life a hydrochephalus was diagnosed in one survivor of the ECMO group. A recurrent diaphragmatic hernia was noted in 4 ECMO survivors of whom 3 underwent a reoperation. In addition to the usual procedures such as cannulation, decannulation and CDH repair in total 35 surgical procedures had to be performed in 16 patients of the ECMO group because of medical and surgical complications (table 4). In the CT group

only 4 procedures, in addition to the usual CDH repair, were performed in 4 patients because of a small bowel obstruction.

Musculoskeletal defomities Chest wall deformity is significant feature after CDH repair in the ECMO group as well as in the control group.

Table 4 **Additional Surgery – Reoperations in the first year**

	ECMO-group	CT-group
Hemorrhage at the surgical site	6	-
Cannula problems (bleeding, clots, dislodgement)	4	-
Small bowel obstruction	4	4
Closure enterostomy	2	-
Removal of abdominal wall patch	6	-
Recurrent diaphragmatic hernia	3	-
Nissen fundoplication	5	-
Ventriculoperitoneal drain	1	-
Peritoneal Dialysis	1	-
Coarctatio aortae repair and reexplorations because of anuria	3	-

Note : More than one complication may be present in 1 patient

Respiratory condition At one year of age the ECMO survivors continue to have more pulmonary problems. Nine children of the ECMO group (60%) displayed breathing difficulties with tachypnea and costosternal retractions at physical examination and were receiving airway medications. Three of them required supplemental oxygen at home.

Growth and nutrition In the ECMO group more feeding problems remained than in the CT group. One patient had an extreme food refusal. Gastroesophageal reflux (GER) was encountered in both groups. However a Nissen fundoplication was performed in four patients of the ECMO group and in none of the CT group during the first year of life. Eleven children (71%) of the ECMO group demonstrated a failure to thrive.

Neurological evaluation No patient had evidence of spasticity or cerebral palsy. The neurological development can be specified as delayed in two survivors of the ECMO group and in three patients of the CT group, namely not achieving the expected developmental milestones on time with abnormal findings on neurological examination. The neurocognitive outcome of ECMO CDH survivors has been assessed more exactly thant in the CT CDH survivors because of the nature of the follow-up study (table 5) Generally the motor skills lagged behind the cognitive skills

Table 5 **Neurodevelopmental outcome at 1 year of age for ECMO survivors : motor quotient by MDI – score**

Motor	Cognitive normal	Cognitive suspect	Cognitive delayed	
normal	5	-	-	5 (33%)
suspect*	4	1	-	5 (33%)
delayed**	1	2	2	5 (33%)
	10 (67%)	3 (20%)	2 (13%)	15(100%)

* suspect 1 SD - 2 SD below mean

** delayed > 2 SD below mean

Only one ECMO survivor had a motor quotient equal to or greater than 1 0. The mean MDI score for this population fell within the normal range 99 (range 55 to 125) The mean MQ score fell more than 1 SD below the norm 0.73 (range 0.55 to 1.0).

Discussion

ECMO has been shown to improve survival for neonates with persistent pulmonary hypertension (PPHN) from diverse causes [1,2,10,13]. Beyond the issue of survival questions arise the concerns of the morbidity, the outcome and the quality of life among the survivors of ECMO. Most reports have focused on the neurodevelopmental outcome in the entire population that survived ECMO without regard to the original underlying disease and without adressing morbidity from causes other than neurodevelopmental impairment [14-17]. In other reports concerning the outcome of neonates with severe respiratory failure treated with or without ECMO patients with congenital diaphragmatic hernia were even excluded from follow-up studies [18,19]. Therefore, the purpose of this study is to describe all sequelae encountered in the

early follow-up of CDH patients, surviving after ECMO-treatment. The outcome of this group of neonates was compared with a group of contemporarily treated CDH patients, surviving without ECMO support The study of this latter group had a retrospective nature. Therefore the data of this group may not be so detailed as that the ECMO group, in which a prospective standardized follow-up was performed The morbidity encountered in the ECMO group is much more than in the CT group, especially, more complications and more additional surgical procedures were observed.

Respiratory outcome

Considering the presence of pulmonary hypoplasia, the intensity of pre-ECMO artificial ventilation, the duration of post ECMO artificial ventilation and the disturbed pulmonary mechanics – in part due to the (almost) complete absence of the hemidiaphragm in many survivors – the presence of chronic lung disease and signs of chronic reactive airway disease amounting to 60% of the population is as to be expected

Up to now little is known about the pulmonary function and respiratory illness in CDH-ECMO-survivors. Extensive studies of respiratory function in children surviving with CDH in the era before ECMO have been published [20 21]. Although spirometric data and ventilation-perfusion (V/Q) radionuclide scans show signs of restrictive lungfunction and V/Q mismatch with particularly a great reduction in perfusion these survivors live generally a normal life and exhibit normal physical activity without subjective complaints These data may however not be applied to this group of patients with pronounced pulmonary hypoplasia, who would not have survived without ECMO. Lund et al in their article about hidden morbidity in high-risk-CDH-survivors report on the "significant disabilities in addition to the chronic lung problems that they may also have", but don't mention the pulmonary sequelae themselves [24] The results at discharge in the present report are comparable to the data reported by Van Meurs in a group of 18 CDH-ECMO-survivors [25]. In that series 12 meet the criterion for chronic lung disease (67%) (receiving oxygen therapy at 28 days of age), 4 were discharged with oxygen at home (18%) and 5 were receiving bronchodilators or diuretics at the time of discharge (23%).

The incidence of CLD upon discharge and chronic respiratory illness at one year of age in CDH-ECMO survivors reported in the present series (60%) is in accordance with other studies[25 28].

Nutritional conditions

The – by many authors – noted growth failure in the CDH-ECMO population has been connected with chronic respiratory problems because of the higher energy expenditure for breathing and because of the poorer sucking and/or swallowing ability [24-29].

However, nutritional disorders encountered in 57% of the ECMO group may also contribute to a poor weight gain of these children. Some infants experience an extreme food refusal. In one patient this food refusal lasted for 5 years. Managing these problems may be difficult according to our experience. Nutritional and respiratory problems appear to be strongly correlated. In a number of patients GER, food refusal, foregut dysmotility, swallowing difficulties, poor sucking ability and/or restricted pulmonary function are hardly distinguishable from each other. GER is one of the main problems seen in association with the increasing survival of severe high risk CDH infants; both for CT treated infants and for ECMO treated infants [25 35]. The reported incidence ranges from 39 to 89% in ECMO CDH survivors and up to 62% in the CT CDH survivors. Foregut dysmotility with food refusal and swallowing difficulties is particularly observed in ECMO CDH survivors [24-32]. The cause of the disturbed motility in the esophagus remains unknown. It is not unimaginable that pressure on the esophagus by herniated viscera and acute kinking of the esophagus by an intrathoracically located stomach may interfere with the blood supply and the prenatal development of the esophagus with resulting impaired motility [29 30,36]. Several factors predisposing to GER may be present in these children such as the disturbed anatomy of the gastroesophageal junction and the raised abdominal pressure after CDH repair [34 35]. In any case in patients with large defects with complete or partial absence of the perihiatal diaphragm it is hard to expect that a normal functioning lower esophageal sphincter (LES) is present [29,31,32,34].

On the basis of their observations Stolar et al drew attention to the functional and the anatomic abnormalities of the esophagus and the lower esophageal sphincter [29,30]. They observed a megaesophagus accompanied by poor esophageal motility in association with GER and polyhydramnios. They supposed that esophageal dilatation seen on postnatal chest X-rays was caused by prenatal kinking of the esophagus leading to polyhydramnios prenatally, and swallowing disorders postnatally. Nagaya et al postulated that infants with severe pulmonary hypoplasia have GER because of deviation of the esophagus to the affected side with shortening of the intra abdominal esophagus and the subsequent creation of a hiatal hernia as lung expansion occurs [32].

Whatever the cause of GER it is clear that GER is present in a large number of CDH ECMO survivors and that GER may be responsible for significant morbidity in this population. Recurrent bronchitis and aspiration pneumonia are wellknown complications of GER whereas bronchospasm may occur as a vagal nerve reflex during acidification of the esophagus [37 38].

Because such pulmonary complications due to GER may be potentially disastrous in this already compromised group of patients an aggressive management of GER might be advocated in order to avoid these complications Although nutritional disorders may be present as a source of morbidity for a long time, it seems that these will resolve with time

Neurodevelopmental outcome

This study displayed neurological abnormalities in about 20% of the survivors, consisting of hearing loss, hydrocephalus, and seizure disorders. One patient who was severely impaired, died before one year of age. None of the survivors had cerebral palsy, spasticity or mental retardation. Mild to moderate developmental delays were demonstrated in 67% of the survivors at one year of age. Usually these delays were characterized by a delay in motor skills with normal cognitive development This delay in motor skills is probably related to the pulmonary condition and to a poor endurance. Only one patient showed a motor development in conformity with calendar age, whereas the neurocognitive outcome was within normal ranges for 67% of the survivors

The interpretation of these findings is difficult for several reasons. Firstly it is not clear whether an unfavourable outcome is attributable to the duration of pretreatment hypoxemia, to the pre-ECMO therapy (such as hyperventilation and alkalization), to the ECMO-treatment itself, to the long hospitalization and the morbidity during the first hospital stay or to the underlying disease or remaining disabilities [2 8 39 40]. Furthermore, it is difficult to compare the results concerning the neurodevelopmental outcome in ECMO CDH survivors with other groups of patients. These ECMO-CDH-survivors can neither be compared to other CDH patients surviving without ECMO nor to other infants, surviving ECMO. Comparison of the results of the present study with those of other published studies is difficult, because differences in outcome may relate to differences in survival. It seems plausible that neurodevelopmental outcome is better as survival is lower in a certain group. Thus far, studies reporting on ECMO-survivors contain often a small amount of CDH patients and limited data on CDH-ECMO-survivors themselves are available [14-17]. Even less information is available on the neurodevelopmental outcome of those infants with high-risk CDH who are treated without ECMO [41]. Davenport reported on the outcome of 23 CDH survivors who had been managed by delayed surgery after a period of stabilization. He observed major disabilities in 2 patients (9%) and minor disabilities in 2 further patients (9%), he noted a mean developmental quotient (DQ) of 108 in this group with no developmental delay (defined as DQ < 70) In a study focused on the outcome of ECMO-treated CDH-patients the neurodevelopment of children with CDH had been reported to be similar to that of all other ECMO-survivors [25] In other studies it was apparent that the CDH-population as a whole fared significantly worse [26-28 42]

Developmental delays have been reported to be present in 46% to 58% of ECMO-CDH-survivors, with severe delays or impairment in 13% to 23% [14-16 24-28 42].

The results of the present study concur remarkably closely with the reported results of CDH-ECMO-survivors in the literature major neurodevelopmental disabilities were noted in 13% of the survivors, the cognitive development is normal in at least 67% of the survivors, whereas 67% of the survivors have a motor delay at 1 year of age [26 28 42]

Nobuhara et al, Bernbaum et al and d'Agostino et al who reported motor delays in their CDH-populations connect this motor delay with the presence of hypotonicity in more than 75% of the survivors at 1 year of age [26 28] This decreased muscle tone affects the lower extremities more than the upper extremities [27].

In the present study the gross motor performance was significantly poorer than the fine motor performance and the motor development in prone position was more delayed than in supine position. Probably this delay in gross motor performance has to attribute to the respiratory restriction that most infants yet have at this stage. So, a different motordevelopmental route was noted However at this moment it is unknown what that means for the later motor outcome (which does not necessarily mean to be worse).

Concluding, (1) the present study shows that the extent and the degree of morbidity in a high risk CDH population surviving due to ECMO are substantial. It seems to be the price for the gain of a higher survival rate. Notwithstanding all kinds of adverse factors, the outlook for these children remains encouraging with a reasonably low incidence of definite disabilities. (2) Taking into account the known mortality and severe disability at 1 year of age, there is little doubt about the benefit of ECMO compared to "conventional" therapy. Even for infants with congenital diaphragmatic hernia. (3) With increasing experience in the management of these CDH-infants it may be expected that morbidity decreases.

Therefore, long-term follow-up in specialized centers with a well-cooperating multidisciplinary team – familiar with the variety of problems encountered – remains essential for improvement in the quality of life for these children and for good support of the parents.

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Part VI

Closing Remarks

Chapter 12

Epilogue

12.1 Introduction

This thesis addresses the impact of the clinical application of ECMO on the management of neonates with Congenital Diaphragmatic Hernia (CDH). An unacceptably high mortality among neonates with CDH despite all new developments in management of CDH patients together with the ongoing reports regarding the successful clinical application of ECMO in these patients stimulated a study for the efficacy of ECMO support in the therapeutical armoury for neonates with CDH.

The most important objectives of the studies presented in this thesis were:

1. Is it possible to predict the outcome of CDH patients?
2. Is ECMO therapy efficacious for CDH patients?
3. With which hazards and adverse sequelae is this aggressive, invasive and potentially life saving therapy attended?
4. What is the morbidity, the neurodevelopmental outcome and the quality of life of the CDH patients who could be salvaged by ECMO?

12.2 Results of the study

1. Risk assessment and outcome prediction Reviewing preoperative chest radiographs of newborns with CDH according to a previously described scoring system we were not able to identify survivors and nonsurvivors. For outcome prediction this X-ray scoring system is not of great value (Chapter 4). Analyzing alveolar to arterial oxygen pressure gradients ($AaDO_2$) linked to time as an entry criterion for ECMO it was proved that $AaDO_2$/time criteria as formulated in the literature could be deceptive for infants with CDH. High $paCO_2$ values are affecting the sensitivity of $AaDO_2$ as entry criterion, so that 53% of the infants who ultimately died should not have become eligible for ECMO support. All CDH patients should have died before ever reaching "classically" formulated $AaDO_2$ entry criteria for ECMO. $AaDO_2$ values may be unreliable for outcome prediction and for ECMO-selection in CDH patients.. (Chapter 5)

2. Efficacy of ECMO in CDH patients The benefit of ECMO in cases of high-risk CDH was studied by comparing pre-ECMO (1987 to1990) and post-ECMO (1991 to1994) 3-month survival statistics. The 3-month survival rate for unstable neonates (who could not be stabilized by conventional therapy) improved from 0% in the pre-ECMO era to 61% in the ECMO-era ($p=0.004$). This highly significant difference showed that ECMO is a very valuable

addition to the management of high-risk CDH patients whose conditions remain unstable despite maximal conventional therapy (chapter 7)

3 Consequences and hazards attending the clinical introduction of ECMO-therapy In the early experience with ECMO in CDH patients significant bleeding complications were encountered at the surgical site (Chapter 6) This complication could successfully be faced by the use of tranexamic acid (Chapter 8) An unexpected complication occurred in a patient with CDH treated with venoarterial ECMO In this patient the clinical course was complicated by the development of an aortic coarctation diagnosed after decannulation and sacrifice of the right common carotid artery Limits to surgical correction of the hypoplastic distal aortic arch were set, because the single left carotid artery could not be clamped (Chapter 9)

4 The outlook and neurodevelopmental outcome After successful ECMO treatment for CDH recurrent hernia was noted more frequently This increase of relapses was attributed to the improved survival of patients with large patch-repaired defects by using ECMO (Chapter 10) Ultimately it was shown that the higher survival achieved by ECMO was obtained at the cost of more morbidity and was attended by pulmonary, gastrointestinal and neurological sequelae However, no patient had evidence of severe neurological impairment at 1 year of age The neurodevelopmental evaluation at 1 year of age was characterized by a mild or moderate delay in motor skills with normal cognitive development (Chapter 11)

12.3 General discussion; the state of the art

In only a few decades the interpretation of congenital diaphragmatic hernia as a purely anatomical defect has turned to a complex pathophysiological problem [1,2] In the early days of paediatric surgery surgical repair of CDH seemed to be a straight forward therapeutic solution Ladd and Gross advocated surgical treatment immediately after birth or as soon as possible, before respiratory problems occurred [1] Early repair should determine the outcome and the poor results were related to delay in surgery However, despite an aggressive attitude the survival rates decreased rather than increased [3,5] In 1969 Young showed that there was an inverse relationship between the age of admission and mortality [5] Earlier diagnosis combined with successful resuscitation and rapid transport to surgical centers resulted in more neonates being admitted and undergoing surgery, who did not have any chance of survival before because of the extent of pulmonary hypoplasia [4]

The high mortality associated with CDH has been shown to be caused by pulmonary hypopla

sia and by persistent pulmonary hypertension [6-11]. The persistent pulmonary hypertension has been considered as the major abnormality in CDH, responsible for the majority of the deaths associated with CDH [10 11]. However, the pulmonary hypoplasia as a cause of death cannot be ruled out and there exist no tests or objective criteria by which the extent of pulmonary hypoplasia can be established. At this moment we are not able to distinguish infants, who have hypoplasia incompatible with life from infants who have a potentially reversible pulmonary hypertension, despite the various criteria which have been proposed to predict the outcome of neonates with CDH [12 22] Nevertheless these criteria may be helpful for risk assessment and may be used for the development of therapeutic strategies.

Monitoring ventilatory parameters it was observed that the clinical condition of the infants was deteriorating rather than improving by reduction of the hernia [23 24]. Based on the observed postoperative deterioration, a strategy of delayed surgery after a preoperative period of ventilatory and hemodynamical stabilization has been introduced [23 26]. However, until now there have been no strict criteria to dictate at which point surgical repair should be performed nor how long surgery should be delayed [27 28]. Until now it has not been clear what is happening during the period of stabilization, although Moffitt et al have tried to study this [29]. Most authors could not show an improved survival with the strategy of delayed surgery nor for that matter a decreased survival [24-26 28 30]. This approach has however gained increasing application in the past decade and has become the standard procedure [31 36] Anyhow, the preoperative period of stabilization provides the opportunity to optimize the clinical condition and to avoid risk factors for the development of a recurrent pulmonary hypertension. Coping with pulmonary hypertension remains an important assignment in CDH patients because PPHN is one of the determining factors of outcome. In the eighties various vasodilators have been advocated and used to diminish the pulmonary vascular tone, if PPHN is present [37 41]. However a specific pulmonary vasodilator was not available and most agents had no or only a temporary effect [39]. At that time the introduction of ECMO provided new opportunities to overcome episodes of persistent pulmonary hypertension [42 43]. Many centers around the world have used ECMO in patients with PPHN with encouraging results, i.e., improved survival rates [44-53]. However, the benefit of ECMO is less evident in CDH-patients [54-59] According to the ELSO registry the survival rate of CDH patients treated by ECMO lagged behind that of other patient groups receiving ECMO such as those suffering from meconium aspiration syndrome (59% vs. 94%) [46]. This lower survival rate stresses again the complexity of the pathology in CDH. Although ECMO is a good therapy for neonates with a PPHN, it is no therapy for newborns with a serious pulmonary hypoplasia, who have no chance of survival after discontinuation of ECMO therapy Maturation of the lungs may not be expected to occur during the limited period of ECMO therapy. Therefore several centers have tried to exclude these newborns

from ECMO treatment by asking for extra entry criteria, for instance a honeymoon period or at least one preductal or postductal PaO_2 of 80 to 100 mmHg (10,7 to 13,3 kPa) [60 61] Although fulfilling one or both extra criteria is a fairly good predictor of a favourable outcome, not-fulfilling of one of these criteria does not necessitate an unfavourable outcome, as the effects of pulmonary hypoplasia cannot be distinguished from the effects of therapeutic efforts such as barotrauma (causing lung injury) and/or hyperhydration [62 63]. As a consequence the application of ECMO has been advocated in all CDH patients for whom conventional treatment does not suffice [62]. However, the increased survival – by applying ECMO in all CDH patients without using extra entry criteria – has to be weighed against the number of patients, in which ECMO treatment was not helpful, because those patients have no chance of survival In these cases ECMO causes unreliable expectations and needless efforts with a waste of scant resources. The benefit of the approach without the use of extra entry criteria (i.e. honeymoon or PaO_2 of 80 to 100 mmHg) seems to be very limited [59 64]. Despite the fact, that over the years already more than 12000 neonates have been treated by ECMO, there is still much controversy regarding its usefulness and clinical application, especially for infants with a primary diagnosis of CDH [65 70]. The debates about the value of ECMO are often confused by varying interpretation of selection criteria and estimates of applied maximal conventional treatment. Because of reluctancy to withhold ECMO therapy with a good survival chance (more than 62%) from children, who were very certain to die without ECMO, the idea of a randomized controlled study was rejected at the beginning of the ECMO program in our institution [71]. Recently the UK Collaborative ECMO Trial Group has however published the results of a randomized trial of neonatal ECMO throughout the United Kingdom [66]. The clinical effectiveness of ECMO was demonstrated with a reduced risk of death or severe disability in all categories of patients. That trial group was not able to give such a pronounced opinion upon the role of ECMO in the management of infants with CDH because of the limited numbers of CDH patients who were enrolled into the study. The results of the present study with 21 survivors at the age of 1 year out of 29 ECMO treated CDH patients (72% survival rate at 1 year of age) compare favourably to the reported results concerning CDH in the UK study with only 4 survivors of 18 ECMO allocated CDH patients (22% survival rate) and put the effectiveness of ECMO (for CDH on the short term)beyond doubt.

From the UK study as well as from the present study it may be concluded, that at this moment for CDH-infants who met criteria for ECMO eligibility (1) continuation of conventional treatment is doomed to failure and (2) ECMO is the best therapy available.

So far ECMO has been reserved as rescue therapy for infants who cannot be stabilized by alternative therapies. Despite the use of ECMO as a last resort therapy – when the alternative therapies are failing – no other new therapy has met such criticism as ECMO [65 67 68 71].

In fact there are few therapeutic modalities for which all aspects of the treatment – selection, clinical application and performance, follow-up and outcome studies, registration and data collection – are so well-documented and have been so strictly laid down by protocol as is the case for ECMO Perhaps these factors are just the basis of the good success of ECMO to a great extent [72] The ELSO and Bartlett may take credit for these aspects of ECMO therapy to themselves.

Since deferred surgery has become the widely accepted approach to the management of CDH, ECMO support has been incorporated as part of the preoperative stabilization [24-36 73 76]. If ECMO is used for stabilization prior to surgery, the question arises when the diaphragmatic defect should be repaired during or after weaning from ECMO support before or after decannulation? [74 77 81]. The timing of surgical repair before decannulation has the advantage that the ECMO circuit acts as a safety net, if recurrent pulmonary hypertension occurs after surgery The disadvantage of repair on ECMO – before decannulation – is the increased risk of bleeding complications [74 80 82]. In our institution we decided to repair the defect on ECMO, late in the ECMO course when the patient had shown to be weanable from ECMO [80]. In this concept PPHN – elicited by the surgical procedure – could be precluded or faced by ECMO support and in case of hemorrhagic complications ECMO could be withdrawn within 24 to 48 hours. By running high ECMO flows during and directly after surgical repair we cannot only prevent PPHN but at the same time we can probably reduce bleeding complications because high ECMO flows allow a lower level of anticoagulation therapy. During surgery major dissections and incidental procedures have been avoided because of the heparinization. Inspite of these measures significant bleedingcomplications were encountered at the surgical site [80]. Adhering to our strategy and noting reports in the literature concerning the use of antifibrinolytic agents for reduction of hemorrhagic complications on ECMO we started with the application of tranexamic acid (TEA) during and after CDH repair [82 84] TEA administration has been proven to be effective for this purpose, but it must be borne in mind that thrombotic complications may occur with the use of antifibrinolytic therapy [84 85]

With regard to the operative repair of the diaphragmatic defect the fundamentals remain the same with or without the use of ECMO. However, two remarkable features were observed in the group of infants who required ECMO for preoperative stabilization these concern the extent of the diaphragmatic defect and the closure of the abdomen. In only 3 out of 28 (11%) ECMO stabilized infants the diaphragmatic defect could be closed by a primary repair. In all other cases (89%) the defect was too large to reapproximate the edges without undue tension, closure was accomplished by synthetic polytetrafluoroethylene (PTFE-Goretex) patch repair. Continuing surgery the scaphoid and mostly undersized abdominal cavity can make primary closure of the abdomen difficult or impossible Closure that create undue tension can compli-

cate the postoperative ventilatory management, can cause a decreased perfusion of the lower extremities and kidneys with a decreased urine output and can compromise the surgical repair resulting in recurrent hernias of the diaphragm and wound dehiscences. For these reasons a PTFE (Goretex) patch repair of the abdominal wall had to be accomplished in 11 of the 28 (39%) ECMO stabilized patients In general there is sufficient room in the abdominal cavity within a few weeks enabling the removal of the abdominal wall patch and the subsequent closure of the laparotomy wound The question relating to the fate of the PTFE diaphragmatic patch with growth remains unanswered for the present [86 91 92]

In recent years several new therapeutic methods have been used in the management of CDH. Surfactant deficiency in CDH has been documented in human studies as well as in the fetal lamb model of CDH [93 95] Two alternative approaches may be tried to correct this deficiency (1). Surfactant replacement therapy has been used by the administration of exogenous bovine surfactant [96 98] In the fetal lamb model improvement in lung compliance and gas exchange as well as reduced pulmonary vascular resistance have been demonstrated by exogenous surfactant therapy [99 100] (2). Another approach is offered by the prenatal administration of glucocorticoids, by which the endogenous surfactant production may be enhanced and by which lung maturation may be accelerated [101 103].

Inhaled Nitric Oxide (NO) has been shown to reduce pulmonary hypertension without systemic hypotension and to increase pulmonary blood flow [104-106]. Although the response to NO in newborns may be very dramatic, not all infants respond. The experience in newborn infants with CDH is still small and the results have been inconsistent

Until recently hyperventilation has been the standard approach to the treatment of PPHN [107 108]. This approach is now being questioned because of the resulting pulmonary barotrauma [109]. Barotrauma appears now to be one of the most frequently encountered causes of death and morbidity [35 36 110]. Hyperventilation can not only cause lung damage, but the concomitant hypocarbia may have inadvertent effects on cerebral circulation, resulting in brain damage[152 154]. Therefore efforts have to be addressed to avoid ventilation-induced injuries. Wung et al advocated a pressure limited ventilation ignoring hyercabia (now commonly known as "permissive hypercapnia ventilation") [109]. Survival rates were reported to be improved with a strategy in which the use of hyperventilation has been abandoned and in which a preductal saturation of greater than 90% has been maintained [35 111 112]. In order to avoid barotrauma it has become more accustomed to increase ventilatory rates rather than to increase airway pressure designated as high frequency positive pressure ventilation (HFPPV) [113 115]. Currently the greatest HFPPV experience in neonates has been gained with high frequency oscilatory ventilation (HFOV) In randomized studies HFOV has appeared to be beneficial compared to conventional ventilation in newborns with respiratory failure [115] No randomized trial has

been done yet in CDH concerning the use of HFOV. Some studies are claiming the efficacy of HFOV for preoperative stabilization in CDH patients with improving survival [116,117]. However, one of the mainstays for the use of HFOV is the hyperventilation-produced alkalosis. Therefore it can be questioned whether HFOV application has great prospects with the increasing awareness of the adverse effects of that approach. Otherwise the reported results with the employment of HFOV in CDH patients are disappointing [113,118,119], in a recent report the survival rate for infants treated by HFOV rescue therapy was only 11 % [36]. So the place of HFOV in the treatment of CDH is still uncertain. The same observation can be applied to intratracheal pulmonary ventilation (ITPV) [120,122]. Partial liquid ventilation has presumably more possibilities to overcome respiratory insufficiency and to avoid lung damage [117,123]. After beneficial findings in experimental animal studies partial liquid ventilation (PLV) with perflurocarbon has been attempted for severe respiratory failure in neonates with CDH while on ECMO [124-127]. More experience with these new therapeutic modalities is required before the clinical usefulness of each of these methods can be elucidated. Because the results of the clinical application of these new therapies are still uncertain, trials studying the value of these new therapies should be restricted to those institutions in which ECMO facilities are available. In case of failure ECMO support can always be provided as a rescue treatment.
All the aforementioned therapies concern the postnatal management of the lung and pulmonary vascular abnormalities. So far pulmonary hypoplasia was accepted as a given fact for which condition no therapy was availabe. However, several authors were able to demonstrate an improvement in lung growth, expansion and maturation after repairing the defect in utero in fetal lamb studies [128,129]. These observations offered new perspectives for the treatment of CDH by fetal surgery [130-133]. Repair of CDH in human fetuses was attempted by Harrison et al but only moderate results in terms of survival were reported [134]. Fetal repair of CDH is technically very difficult. A less invasive fetal procedure consisted of tracheal ligation, by which the effects of pulmonary hypoplasia in the lamb model could be prevented and corrected [135-137]. Fetal tracheal ligation may be accomplished by endoscopic surgery [138-140].

Follow up studies of CDH patients treated with conventional therapy in the past did not suggest much morbidity among the survivors [141-144]. Even the pulmonary sequelae in these patients turned out to be better than was expected and were not interfering with acitivities of daily life. On the contrary preliminary follow-up studies of CDH patients treated with ECMO suggest more morbidity, namely gastroesophageal reflux, feeding problems, hearing loss, neurological impairment, chest wall deformities and scoliosis among these survivors [145-149]. In spite of ECMO therapy up to 60% of the infants appears to have chronic pulmonary disease due to pulmonary hypoplasia and/or pulmonary injury (barotrauma). ECMO support has

resulted in a higher survival rate especially in children with large defects in whom a prosthetic replacement is required [87 88 150 151] However in this group of patients a higher rate of recurrent hernias has been encountered [88] Thus it seems that an increasing morbidity rate is the price for a decreasing mortality rate Together with more morbidity other kinds of complications and problems are met which were not seen before More morbidity and more complications may be responsible for a declining quality of life That in its turn may put forward questions about the benefit of an improved survival Concomitantly that raises the dilemma whether ECMO support as a rescue therapy should be applied earlier and in every infant with a CDH, or whether ECMO support should be withheld from certain infants

12.4 Conclusion

At present we believe that

(1) ECMO as rescue therapy is a valuable addition to our treatment arsenal for CDH patients,

(2) The morbidity and the adverse sequelae occurring in consequence of survival with ECMO don't outweighed the increased survival itself, gained by ECMO,

(3) ECMO has only to be offered to strictly selected patients

Studying ECMO and CDH it becomes clear that

1 Several clinical problems associated with CDH have not yet been elucidated

2 The management of both strongly interrelated pathophysiological mechanisms of CDH (pulmonary hypoplasia and elevated pulmonary vascular resistance) is difficult despite the great variety of therapeutic options

3 Consequently the best therapeutic approach for CDH patients with a poorer prognosis has yet to be evolved

4 PPHN in newborns with CDH is a more complex problem than PPHN in newborns with other underlying conditions

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Summary

This thesis deals with the clinical aspects of congenital diaphragmatic hernia (CDH) and the application of extracorporeal membrane oxygenation (ECMO) in the management of neonates with CDH By congenital diaphragmatic hernia is meant the posterolateral diaphragmatic defect, also designated as the hernia of Bochdalek. It entails a developmental defect in which the usual closing proces of the diaphragm has been arrested or disturbed before birth Because there is no (complete) separation between the thoracic and abdominal cavities the abdominal viscera migrate unhindered into the thorax This condition (CDH) remains a critical problem in neonatal surgery because respiratory failure occurring immediately after birth is responsible for the death of 40 to 60% of the newborns with this anomaly. Initially it was thought that the respiratory distress was caused by the protruded intestines by which the lungs were compressed and were unable to inflate themselves The solution of the problem seem to be straight forward the allevation of the pulmonary embarassment by removal of the intestines from the thoracic cavity and an ensuing surgical repair of the diaphragmatic defect
However the underlying pathophysiological condition turned out to be more complex than a purely mechanical problem on the basis of a simple anatomical defect. The pathophysiology is not yet fully understood but currently it is generally assumed that pulmonary hypoplasia and pulmonary hypertension are the main pathophysiological phenomena responsible for the respiratory distress and the high mortality in CDH patients.
Although the term hypoplasia is not well defined, by pulmonary hypoplasia is meant an underdevelopment of the lungs. This underdevelopment concerns not only a reduced lung weight in reference to the body weight, but also a defective development of each of the functional systems within the lungs· conducting airways, gas exchange surfaces, air-blood interfaces, surfactant system, antioxidant defense system and last but not least pulmonary vasculature. The underdevelopment of the pulmonary vascular bed consisting of a reduced number of arterial vessels and concomitantly of an increased muscle mass in the vessel wall, form the morphological basis for the pulmonary hypertension. In this condition of persistent pulmonary hypertension of the newborn (PPHN) diverse factors (among which hypoxia and acidosis) have an effect on the anatomically abnormal pulmonary vasculature, that reacts with vasoconstriction and consequently with a rise in the pulmonary vascular resistance As a result of the increased pulmonary resistance the pulmonary blood flow shunts from right-to-left to the systemic circulation. That induces a gradually increasing oxygenation problem for the infant and leads ultimately to death. Management strategies were adapted according to what was known of the pathophysiology. These aspects of CDH are discussed in **Chapter 1.**
Generally pulmonary hypoplasia was considered as a given condition for which condition no therapy was available. Infants who have a severe pulmonary hypoplasia can never be adequately oxygenated and die shortly after birth regardless of the kind of treatment Therefore

therapeutic protocols focused on the manipulation of the pulmonary hypertension. Therapeutic efforts were adressed to avoid risk factors and conditions which might trigger increasing pulmonary vascular resistance such as hypoxemia, acidemia, alveolar hypoxia and increased transpulmonary pressures. If pulmonary hypertension developed in spite of all these measures several vasodilators were administered in an attempt to reduce pulmonary vascular resistance and concomitantly to reduce right-to-left shunting. Emergency surgery was replaced by deferred surgery after a period of cardiorespiratory stabilization.

The introduction of extracorporeal membrane oxygenation (ECMO) provided new opportunities to reverse pulmonary hypertension for those infants in whom all conventional therapies had failed Clinical aspects of ECMO therapy are discussed in **Chapter 2** ECMO is the process of temporary but prolonged gas exchange (especially oxygenation) outside the body across a semipermiable membrane (membrane oxygenator=artificial lung) by the use of extracorporeal circulation For the ECMO application infants have to be connected to the ECMO circuit. Using veno-arterial (VA) ECMO cannulas are placed into the right common carotid artery and the right internal jugular vein. As a consequence cerebral circulation through both vessels is interrupted temporary or permanently. During ECMO support blood is drained from the right atrium to the circuit and returns into the systemic circulation after oxygenation in the membrane oxygenator. Therefore systemic anticoagulation has to be maintained during the whole course of ECMO in order to prevent clot formation as a result of the contact of blood with foreign surfaces. The use of systemic heparinization however, exposes the already compromised infants to the risk of bleeding complications, particularly intracranial hemorrhage.

The high mortality among neonates with CDH despite all advances in the management of these infants together with ongoing reports on the succesful clinical application of ECMO was the motivation behind to this study of which the objectives are described in **Chapter 3.**

Because of the invasive nature of ECMO and the potential risks associated with ECMO, ECMO treatment must be confined to those infants who are thought to have a high risk of death on continuing with conventional treatment and a low risk of complications upon initiation of ECMO. However, selection of the "appropriate" patients for an "appropriate" therapy may be difficult, especially for a complicated and riskful procedure such as ECMO Through the years several investigators have attempted to identify high risk CDH infants for whom a more agressive therapy has to be instituted In **Chapter 4** we tried retrospectively to identify patients with a high-risk of death by means of a previously described X-ray scoring system of

preoperative chest radiographs. Reviewing preoperative chest radiographs of 33 newborns who were operated because of CDH within 24 hours after birth we were not able to identify survivors and non-survivors according to that scoring system.

In **Chapter 5** we studied retrospectively the alveolar to arterial oxygen difference ($AaDO_2$) linked to time as an entry criterion for ECMO in 60 neonates with respiratory failure 30 neonates who were treated for meconium aspiration syndrome, respiratory distress syndrome, sepsis or idiopathic PPHN (pediatric group) and 30 neonates who had a CDH. It was proven that the $AaDO_2$ time criteria as formulated in the literature were reliable for the infants of the pediatric group but not for neonates with CDH. Fourtyseven percent of the CDH infants died before reaching formulated ECMO entry criteria. Thus, 53% of the CDH patients would be selected too late for ECMO, when we adhere to the published $AaDO_2$ time criteria $AaDO_2$ time criteria may therefore be unreliable as an entry criterion for ECMO in neonates with CDH.

In **Chapter 6** we describe the early experiences with ECMO in CDH patients in our institution. These CDH patients were treated by a strategy of delayed surgery after a period of preoperative stabilization, in which ECMO was incorporated if necessary. All patients who required ECMO for preoperative stabilization and who underwent diaphragmatic repair while on ECMO had bleeding complications. Conceptual adjustments of this approach are discussed, because bleeding complications had an adverse effect to the outcome of these CDH patients.

In **Chapter 7** the benefit of ECMO in cases of high-risk CDH was studied by comparing pre-ECMO (1987 through 1990) and post-ECMO (January 1991 through July 1994) three months survival statistics. During the entire study period (December 1987 through July 1994) all patients who presented in respiratory distress within 6 hours after birth were treated by the same protocol of preoperative stabilization and delayed surgery, the only difference was the addition of ECMO beginning in January 1991. The patients (18 in the pre-ECMO era and 37 in the ECMO era) were stratified based on the response to conventional treatment (1) irretrievable, (2) stable and (3) unstable. The 3 months survival rate for the unstable neonates (who could not be stabilized by conventional therapy) improved from 0% (0 of 9) in the pre ECMO era to 61% (11 of 18) in the ECMO era ($p=0.004$). Based on this highly significant difference it was concluded that ECMO is a very valuable addition to the management of high-risk CDH patients.

Because all patients who required ECMO support for preoperative stabilization and in whom the diaphragmatic defect was repaired while on ECMO suffered from bleeding complications we introduced the use of antifibrinolytic therapy with tranexamic acid (TEA) into the treatment protocol In **Chapter 8** the efficacy of TEA was studied in an unblinded study using historical controls by comparing the postoperative blood loss and the transfusion requirements of red blood cells (RBC) in patient groups treated without (n=9) and with TEA (n=10) Patients who received TEA had significantly less bleeding at the surgical site (59 versus 390 ml, p=0 005) and had significantly lower RBC transfusion requirements than patients not receiving TEA (1.13 versus 2 95 ml/kg/h, p=0.03). It was concluded that TEA is effective in reducing hemorrhagic complications and RBC transfusion requirements associated with CDH repair on ECMO and that the higher survival rate in the TEA treated group might be attributed to the decreased occurrence of severe hemorrhages

In **Chapter 9** an unexpected complication is described occurring in a patient with CDH after decannulation from venoarterial (VA) ECMO. This patient developed an aortic coarctation. Because of the sacrifice of the right common carotid artery due to VA-ECMO treatment the single left carotid artery could not be clamped during the surgical correction of the aortic coarctation This fact limited the surgical resection of the aortic coarctation and the hypoplastic distal aortic arch.

After successful ECMO treatment for CDH patients recurrent hernia was noted more frequently. This observation gave rise to a retrospective study in which we attempted to identify risk factors for a recurrence. The results of this study are described in **Chapter 10.** The medical records of 66 CDH survivors were reviewed. Fiftyseven patients had a left sided defect and 9 paitents a right sided defect. The diaphragmatic defect was repaired by primary suture in 54 patients and by a prosthetic patch closure in 12 patients. Conventional mechanical ventilation with pharmacological support sufficed in 55 patients, whereas 11 patients required ECMO support The defects were divided into 3 groups according to the dimensions of the defect (small, moderate or large). Nine patients (14%) developed a recurrent hernia on the average of 4.0 months after the initial repair. Recurrences occurred: (1) in 5 patients with a left sided defect (9%) and in 4 patients with a right sided defect (44%), (2) in 4 patients with a primary repair (7%) and in 5 patients with a prosthetic patch repair (42%), (3) in 5 patients who were treated conventionally (9%) and in 4 patients who required ECMO support (36%) and (4) in 5 patients with a small or moderate defect (8%) and in all 4 patients with a large defect (100%). So, large patch-repaired right sided defects in patients who required ECMO stabilization are at risk for the development of a recurrence.

Beyond the issue of survival arise the concerns of the morbidity, the outcome and the quality of life for the patients who are surviving due to ECMO support. The outcome and early morbidity of these survivors are described in **Chapter 11** and are compared with the outcome and early morbidity of CDH survivors who received conventional treatment in the same period (January 1991 through December 1996). Twentythree survivors out of 29 ECMO treated CDH infants were enrolled in a routine ECMO evaluation program, whereas 15 of 17 survivors who recovered on conventional treatment (CT) could be followed retrospectively The evaluation was divided into 4 parts. (1) medical and surgical complications, (2) respiratory condition, (3) growth and nutritional status and (4) neurological and developmental outcome. Much more complications were noted in the ECMO group than in the CT group during the first admission. Chronic lung disease upon discharge and chronic respiratory illness at 1 year of age were encountered in respectively 61% and 60% of the ECMO survivors and in 20% and 36% of the CT survivors. The weight of many CDH survivors was below the 10th percentile upon discharge and at one year of age respectively in 87% and 73% of the ECMO group and in 47% and 45% of the CT group Nutritional disorders (such as need for tubefeeding, gastroesophageal reflux and swallowing problems) were noted in 57% of the ECMO survivors upon discharge and remained in 27% of them throughout the first year of life. Neurological abnormalities at one year of age were met in 20% of the ECMO survivors and in 36% of the CT survivors. In the ECMO group the motor development was normal in only 33% of the children whereas the cognitive development was normal in 67% of the children. The average mental development score for the ECMO group fell within the normal range 99 (range 55 to 125). The average motor development score fell more than one standard deviation below the norm: 0.73 (range 0.55 to 1.0). The delay in gross motor performance was related to respiratory restrictions which these infants still have at that age. In conclusion (1) the morbidity in high-risk CDH patients surviving due to ECMO is substantial and more than in these patients surviving with conventional treatment. However the outlook for these children remains encouraging with a reasonably low incidence of definite disabilities, and (2) taking into account the known mortality and the severe disability (impairment) at one year of age there is little doubt about the benefit of ECMO compared to conventional therapy for these high-risk CDH infants.

Conclusions

1. ECMO as rescue therapy is a valuable addition to our treatment arsenal for CDH patients.
2. The morbidity and the adverse sequalae occurring in consequence of survival with ECMO don't outweigh the increased survival itself gained by ECMO.
3. Several clinical problems associated with CDH have not yet been elucidated. Consequently the best therapeutic approach for CDH patients with a poor prognosis has yet to be evolved.

Samenvatting

Congenitale hernia diafragmatica (CHD) is een aangeboren afwijking van het middenrif, die bij ongeveer 1 op 3000 à 4000 pasgeborenen voorkomt. Bij een CHD is er sprake van een storing in het gebruikelijke sluitingsproces van het middenrif tijdens de foetale ontwikkeling, waardoor geen (volledige) scheiding plaatsvindt tussen borst- en buikholte. Als gevolg daarvan kunnen de buikorganen zich nestelen in de borstholte. Ondanks de vele verbeteringen die zich hebben voorgedaan in de behandeling en zorg van pasgeborenen sterft nog steeds 40 tot 60% van de kinderen die geboren worden met een middenrifdefect als gevolg van ernstige ademhalingsmoeilijkheden. Aanvankelijk is gedacht dat de ademhalingsmoeilijkheden na de geboorte veroorzaakt werden door druk van de darmen op de longen. De darmen vullen zich na de geboorte met lucht en als gevolg daarvan kunnen de longen zich niet ontplooien. De oplossing van het probleem leek derhalve simpel en puur chirurgisch. De darmen moesten teruggehaald worden uit de borstholte en het middenrif moest gesloten worden. In de loop der jaren is echter duidelijk geworden dat de pathofysiologie bij een CHD veel ingewikkelder is dan een puur mechanisch probleem op basis van een simpel sluitingsdefect. Waarschijnlijk is het sluitingsdefect slechts van ondergeschikt belang. Twee andere belangrijkere pathofysiologische processen lijken de prognose te bepalen van de kinderen met een CHD: de aanwezigheid van een longhypoplasie en het optreden van een pulmonale hypertensie. Onder longhypoplasie verstaan we een algemene onderontwikkeling van de long tijdens de zwangerschap. De longen zijn daardoor in aanleg te klein, het aantal vertakkingen van de luchtwegen en van de bloedvaten in de longen is sterk verminderd en ook het aantal longblaasjes, waar de gaswisseling plaatsvindt, is afgenomen. Bovendien hebben de bloedvaten in de longen bij CHD-kinderen een afwijkende structuur: de spierlaag in de wand van de bloedvaten is sterk verdikt, terwijl de kleinere bloedvaatjes, die normaal een elastische bekleding hebben, ook omgeven worden door spierweefsel. Als gevolg van deze abnormale structuur hebben de longvaten een verhoogde neiging zich samen te trekken (vasoconstrictie), waardoor de bloedstroom door het longvaatbed wordt belemmerd. Dit kan leiden tot een verhoogde bloeddruk in het longvaatbed (pulmonale hypertensie). Als gevolg van de pulmonale hypertensie kan er een shunting optreden van het bloed vanuit de longcirculatie naar de systemische circulatie. De longdoorbloeding zal daardoor afnemen, zodat ook de gaswisseling in de longen zal afnemen. Er ontstaat een geleidelijk in ernst toenemend zuurstofgebrek, waardoor het kind uiteindelijk komt te overlijden. In de loop der jaren is de behandeling van kinderen met een CHD aangepast aan de veranderende inzichten in de pathofysiologie. Algemeen werd aangenomen dat aan de gestoorde foetale ontwikkeling van de long niets gedaan kon worden: de longhypoplasie was een gegeven feit. Een ernstige longhypoplasie was onverenigbaar met het leven en ondanks alle therapeutische inspanningen zouden deze kinderen toch overlijden. De aandacht in de behandeling werd derhalve meer gericht op het voorkómen en bestrijden

van de pulmonale hypertensie. Factoren die aanleiding zouden kunnen geven tot het optreden van een pulmonale hypertensie zouden vermeden moeten worden. Het idee van een spoedoperatie werd verlaten. Het sluiten van het defect in het middenrif werd uitgesteld tot een later tijdstip, nadat de toestand van het kind was gestabiliseerd. Indien er toch een pulmonale hypertensie optrad werd getracht de opgetreden vasoconstrictie te bestrijden langs farmacologische weg Vele vaatverwijders zijn geprobeerd, maar uiteindelijk werkte geen van deze vaatverwijders specifiek op de longvaten en hadden deze vaatverwijders in het algemeen slechts een tijdelijk effect De pathofysiologische aspecten en de daaraan gekoppelde inzichten in de behandeling van kinderen met een CHD worden besproken in **hoofdstuk 1**.

De invoering van extracorporele membraanoxygenatie (ECMO) bood in de tachtiger jaren nieuwe perspectieven voor het bestrijden van een ernstige pulmonale hypertensie. Tijdens ECMO vindt er gedurende langere tijd gaswisseling plaats buiten het lichaam in een kunstlong (de membraanoxygenator), waarvoor gebruik wordt gemaakt van een bloedsomloop buiten het lichaam (extracorporele circulatie). Voor de toepassing van ECMO moeten kinderen aangesloten worden op het ECMO-circuit. Bij de tot op heden meest toegepaste veno-arteriele (VA) ECMO methode worden daartoe slangen (canules) ingebracht in de rechter halsader (vena jugularis interna) en rechter halsslagader (arteria carotis communis). Gedurende de ECMO-behandeling wordt het bloed via de canule in de halsader afgevoerd naar het ECMO-circuit en nadat er gaswisseling heeft plaatsgevonden in de kunstlong keert het bloed weer terug in het lichaam via de canule in de halsslagader. Als gevolg van het inbrengen van deze canules in de halsader en halsslagader is de bloedstroom naar de hersenen via de rechter hals tijdelijk of permanent onderbroken. Omdat gedurende de ECMO-behandeling het bloed in contact komt met vreemd lichaams materiaal moet systematische antistollings behandeling worden ingesteld, teneinde stolselvorming van het bloed te voorkomen. Het gebruik van antistollingstherapie (heparinisatie) kan echter leiden tot ernstige bloedings complicaties, met name hersenbloedingen. In **hoofdstuk 2** worden de principes van ECMO-behandeling beschreven.

De hoge sterfte onder pasgeborenen met een CHD en de berichten in de literatuur omtrent de gunstige behandeling van ECMO bij zuigelingen in geval van een pulmonale hypertensie vormden de aanleiding voor deze studie (**hoofdstuk 3**).

Gezien het invasieve karakter van een ECMO-behandeling en gezien de potentiele risico's van een ECMO-behandeling is een nauwkeurige selectie van patienten die in aanmerking komen voor een ECMO-behandeling van groot belang. ECMO-behandeling zou slechts toegepast

moeten worden bij die kinderen, die vrijwel zeker zouden overlijden bij het voortzetten van de conventionele behandeling. Anderzijds moeten die kinderen, die ook zonder ECMO-behandeling zouden overleven, uitgesloten worden van een ECMO-behandeling.
Vele onderzoekers hebben in de afgelopen decennia gezocht naar parameters, op grond waarvan men de prognose voor kinderen met een CHD kon bepalen en op grond waarvan men de ernst van de aandoening kon vastleggen. In **hoofdstuk 4** wordt een studie beschreven waarin getracht wordt de prognose van zuigelingen met een CHD te bepalen aan de hand van röntgenfoto's volgens een eerder in de literatuur beschreven scoringssysteem. Hiertoe werden pre-operatieve röntgenfoto's bekeken van 33 pasgeborenen, die binnen 24 uur na de geboorte werden geopereerd wegens een CHD. Op grond van dit röntgenologische scoringssysteem waren wij niet in staat een scheiding aan te brengen tussen kinderen die niet zouden overleven en kinderen die wel zouden overleven.

In **hoofdstuk 5** is nagegaan of de alveolaire arteriële zuurstofgradiënt ($AaDO_2$) gekoppeld aan de tijd bruikbaar was als toegangscriterium voor ECMO-behandeling. Bloedgasanalyses van 60 pasgeborenen met ademhalingsmoeilijkheden werden uitgezet in de tijd: 30 pasgeborenen die behandeld waren voor een meconiumaspiratie syndroom, een respiratory distress syndroom, sepsis of idiopathische pulmonale hypertensie (pediatrische groep) en 30 pasgeborenen met een CHD. Uit dit onderzoek kwam naar voren dat de $AaDO_2$ gekoppeld aan de tijd als toegangscriterium voor ECMO betrouwbaar was voor alle pasgeborenen in de pediatrische groep. Voor kinderen met een CHD bleek dit toegangscriterium ontoereikend: 47% van de pasgeborenen met een CHD stierf alvorens het vastgestelde ECMO-toegangscriterium werd bereikt. Dientengevolge zou 53% van de pasgeborenen met een CHD te laat geselecteerd worden voor een ECMO-behandeling.

In **hoofdstuk 6** worden onze eerste ervaringen met ECMO in het kader van de behandeling van pasgeborenen met een hernia diafragmatica beschreven.. Het behandelingsplan voor deze kinderen bestond uit een uitgestelde operatieve sluiting van het middenrifdefect na een periode van preoperatieve stabilisatie. Voor stabilisatie werd zonodig gebruik gemaakt van ECMO. Indien ECMO nodig was voor preoperatieve stabilisatie dan werd het diafragmadefect gesloten gedurende de ECMO-behandeling. Bij alle kinderen, die preoperatief slechts gestabiliseerd konden worden dankzij ECMO en bij wie het middenrifdefect werd gesloten tijdens de ECMO-behandeling, traden ernstige bloedingscomplicaties op. Onder die kinderen, welke bloedingscomplicaties hadden was de sterfte hoog (60%). Het leek derhalve wenselijk ons behandelingsprotocol aan te passen.

In **hoofdstuk 7** wordt de waarde van de ECMO-behandeling voor kinderen met een CHD nagegaan. Gekeken werd naar de overleving op de leeftijd van 3 maanden. Twee groepen kinderen met een CHD werden vergeleken (1) kinderen behandeld in de periode voorafgaande aan ECMO (1987-1990) en (2) kinderen behandeld in de periode waarin ECMO-behandeling ter beschikking stond (1991-1994) Gedurende de hele studieperiode (december 1987 tot juli 1994) werden alle patientjes, die binnen zes uur na de geboorte ernstige ademhalingsproblemen hadden als gevolg van een CHD, behandeld volgens hetzelfde protocol van preoperatieve stabilisatie en uitgestelde chirurgische therapie. Het enige verschil betrof de toevoeging van ECMO in het behandelingsprotocol vanaf januari 1991. Alle patienten (18 in de pre-ECMO periode en 37 in de ECMO-periode) werden ingedeeld in drie categorieen, afhankelijk van hun reactie op de ingestelde conventionele behandeling. Uit dit onderzoek bleek dat voor die patientjes, die preoperatief niet gestabiliseerd konden worden door middel van conventionele behandeling de overlevingskans toenam van 0% (0 overlevenden op 9 pasgeborenen) in de pre-ECMO periode tot 61% (11 overlevenden onder 18 patientjes) in de ECMO-periode. ECMO kan derhalve gezien worden als een waardevolle aanvulling op de behandelingsmogelijkheden voor kinderen met een CHD.

Aangezien bij alle kinderen, die slechts gestabiliseerd konden worden dankzij ECMO-behandeling en bij wie het middenrifdefect gesloten werd tijdens de ECMO-behandeling, ernstige bloedingscomplicaties optraden werd het gebruik van tranexaminezuur (TEA) ingevoerd in het behandelingsplan voor kinderen met een CHD. In **hoofdstuk 8** wordt de effectiviteit van TEA nagegaan in een open studie, met gebruik van historische controles. Het postoperatieve bloedverlies en de transfusiebehoefte aan rode bloedcellen (RBC's) werden bestudeerd in twee patientengroepen. (1) patienten die geen TEA kregen (n=9) en (2) patienten die TEA kregen (n=10). Het bleek dat patienten die TEA kregen veel minder postoperatief bloedverlies hadden (59 versus 390 ml) en een geringe RBC-transfusiebehoefte hadden dan patienten die geen TEA kregen (1.13 versus 2.95 mg/kg/hr) TEA bleek derhalve effectief in het voorkomen van bloedingscomplicaties, die kunnen optreden bij de chirurgische behandeling van het middenrifdefect tijdens ECMO.

In **hoofdstuk 9** wordt een onverwachte complicatie beschreven die optrad bij een patientje met een CHD na VA ECMO-behandeling. Dit patientje ontwikkelde een coarctatie van de aorta. Als gevolg van de toegepaste VA ECMO-behandeling was de rechter halsslagader onderbonden Bij resectie van de coarctatie en de hypoplastische aortaboog werden beperkingen ondervonden in de chirurgische behandeling, omdat de linker halsslagader niet afgeklemd kon worden.

Na de invoering van ECMO-behandeling werden meer kinderen met een recidief hernia diaphragmatica gezien. Dit vormde de aanleiding tot een retrospectieve studie, waarin risicofactoren werden nagegaan voor het optreden van een recidief CHD. Resultaten van dit onderzoek worden beschreven in **hoofdstuk 10**. De medische dossiers van 66 CHD kinderen werden bekeken. Onderverdeling van de patientjes vond plaats op basis van (1) links- of rechtszijdig middenrifdefect, (2) de mogelijkheid van primaire sluiting van het middenrifdefect of het gebruik van een kunststof materiaal voor het sluiten van het defect, (3) de grootte van het middenrifdefect en (4) conventionele behandeling of ECMO-behandeling. Op grond van dit onderzoek bleek, dat rechtszijdige en grote, met behulp van kunststof materiaal gerepareerde defecten bij patienten die ECMO-behandeling ondergingen een grotere kans hebben op het ontwikkelen van een recidief

Nu met ECMO steeds meer patientjes met een CHD overleven, met name kinderen met grote middenrif defecten komen er ook meer vragen over de kwaliteit van overleving en over de mogelijk nadelige effecten van de ECMO-behandeling. In **hoofdstuk 11** wordt de korte termijn follow-up besproken van CHD-kinderen die overleefden dankzij ECMO-behandeling. Er wordt daarbij een vergelijking gemaakt met de korte termijn follow-up van CHD-kinderen die in dezelfde periode (januari 1991-december 1996) overleefden met conventionele behandeling. De 23 overlevenden van de 29 ECMO behandelde kinderen werden opgenomen in een standaard ECMO-evaluatie protocol, zoals dit was vastgesteld voor de invoering van ECMO-behandeling. Vijftien van de 17 CHD-kinderen die overleefden met conventionele behandeling (CB) konden meegenomen worden in een retrospectief follow-up onderzoek In de ECMO-groep werden meer complicaties vastgesteld dan in de CT-groep gedurende de eerste opnameperiode. Longproblemen bleken bij de ECMO behandelde kinderen vaker voor te komen dan bij de conventioneel behandelde kinderen (plm. 60% ten opzichte van 20 à 36%). De groei van de meeste CHD-patientjes bleek te stagneren. Bij ontslag en op de leeftijd van 1 jaar waren respectievelijk 87% en 73% van de ECMO behandelde kinderen onder de P10 van de gewichtscurve en respectievelijk 47% en 45% van de conventioneel behandelde kinderen. Voedingsproblemen, waaronder de noodzaak voor sondevoeding, de aanwezigheid van gastro-oesophageale reflux en slikproblemen werden vastgesteld bij 57% van de kinderen die behandeld werden met ECMO. Neurologische problemen op de leeftijd van 1 jaar bleken bij 20% van de ECMO-kinderen en bij 36% van de conventioneel behandelde kinderen aanwezig te zijn. De mentale ontwikkeling van de kinderen die met ECMO behandeld waren was in 67% van de gevallen normaal. De gemiddelde mentale ontwikkelingsscore voor de ECMO-kinderen was vergelijkbaar met die van normale leeftijdgenootjes· 99 (range 55-125) Opvallend was de achterstand in motorische ontwikkeling bij de CHD-kinderen, die dankzij ECMO

overleefden. In slechts 33% van de gevallen kon de motorische ontwikkeling als normaal geduid worden De gemiddelde motorische ontwikkelingsscore van deze kinderen viel meer dan één standaarddeviatie onder de gemiddelde norm van leeftijdgenootjes 0.73 (range 0.55 tot 1.0)
Deze bevindingen geven aan dat meer morbiditeit de prijs is voor de betere overleving. Met name ondervinden de CHD kinderen die dankzij ECMO overleven in de eerste opname periode meer complicaties en in het eerste levensjaar meer voedings- en ademhalingsproblemen dan CHD kinderen die zonder ECMO overleven. Als gevolg van deze ademhalings- (en voedings)problemen blijft de motorische ontwikkeling in het eerste levensjaar achter ten opzichte van leeftijdgenootjes De mentale ontwikkeling van deze kinderen lijkt echter goed te zijn Er komen vooralsnog niet meer neurologische stoornissen voor onder de CHD kinderen die overleven met ECMO dan onder de CHD kinderen die overleven zonder ECMO. Deze kinderen lijken derhalve toch een goed levensperspectief te hebben.

Conclusies

In dit proefschrift wordt aangetoond dat ECMO de levenskansen voor kinderen met een aangeboren middenrifdefect verhoogt. De verbeterde overleving gaat ten koste van meer morbiditeit Vrijwel alle kinderen met een middenrifdefect die dankzij ECMO overleven hebben óf complicaties en nog meerdere operaties tijdens de eerste opnameperiode, óf hebben "restverschijnselen" in het eerste levensjaar in de vorm van voedings- en/of ademhalingsproblemen, gepaard gaande met een vertraagde motorische ontwikkeling. Deze complicaties en problemen vormen (soms) een zware belasting voor de ouders. Vooralsnog lijken echter de vooruitzichten voor deze kinderen goed te zijn. Er worden niet meer neurologische problemen gezien bij deze kinderen dan bij andere kinderen die in de neonatale fase medische en/of chirurgische behandeling hebben ondergaan. De mentale ontwikkeling van deze kinderen lijkt gelijkwaardig te zijn aan die van leeftijdgenootjes.

Dankwoord

Bewust of onbewust hebben velen meegewerkt aan de totstandkoming van dit proefschrift.Veel woorden van dank zouden derhalve gesproken moeten worden. Het is echter onmogelijk ieder individueel te bedanken, zonder daarbij iemand "over het hoofd te zien". Zonder daarbij iemand te kort doen, wil ik een aantal mensen in het bijzonder bedanken.
In de eerste plaats geldt dit voor de beide promotores.
Prof. Dr. C. Festen, beste Kees, mijn bewondering voor jouw gedrevenheid en voor jouw persoonlijke inzet en zorg voor patientjes heeft mij destijds mede doen kiezen voor de kinderchirurgie. Ik had het gevoel, dat ik nog veel van je kon leren en dat er nog veel patientgebonden onderzoek gedaan kon worden. Toch heeft het nog tien jaren moeten duren alvorens wij het patientgebonden onderzoek zodanig gestalte konden geven dat daaruit dit proefschrift kon voortkomen. Jij was de initiator van "ECMO Nijmegen". ECMO als project voor ontwikkelingsgeneeskundig onderzoek werd met jou als projectleider naar Nijmegen gehaald. Jouw nauwgezetheid en niets aan het toeval overlatende streven naar perfectie hebben geleid tot een uitstekend klinisch ECMO program.
Dr. W.B. Geven, beste Wil, je bent in de afgelopen jaren een belangrijk gezicht geweest van ECMO Nijmegen. Soms duidelijk zichtbaar en merkbaar, maar vaak ook onzichtbaar achter de schermen heb je je ingezet voor het hele ECMO gebeuren op vele fronten, vaak tot in de kleinste details. Jouw kennis van de long- en ECMO-physiologie is onmisbaar geweest bij de opzet van het ECMO program en is mede verantwoordelijk geweest voor de gunstige ECMO resultaten in Nijmegen. Nu je een andere weg hebt ingeslagen, zullen wij het zonder die motor en zonder dat brein moeten stellen. Wij hopen de komende jaren zonder jou de ingezette lijn vast te kunnen houden.
Drs. A.F.J. de Haan, beste Ton, jouw kijk op cijfers was verbazingwekkend; op sommige momenten ontwapenend, op andere momenten geestverruimend. Op grond van je analyse van cijfers en getallen trok jij conclusies en deed jij vaak voorstellen voor de klinsche behandeling, die uit de mond van een ervaren clinicus konden komen. Je zorgde steeds voor nieuwe openingen, indien ik vast dreigde te lopen in de rijstebrij van gegevens. Je stimulerende werking is van groot belang geweest in de voltooiing van dit werkstuk.
Drs. G. Fons, beste Guus, jij hebt de grondslag gelegd voor het databestand van ons ECMO program. Je hebt daarmee een belangrijke bijdrage geleverd om de trein, die moest leiden tot dit proefschrift, op het spoor te zetten. Je betrokkenheid was hartverwarmend. Jouw efficiënte, nuchtere en "kraakheldere" werkwijze was verfrissend, je humor gaf veel kleur aan het ECMO gebeuren.
Leden van de voormalige ECMO wetenschapscommissie, Prof. Dr. B. Oeseburg en Prof.

Dr.R.C.A. Sengers, beste Berend en beste Rob, voor de belangstelling van de wetenschappelijke vorderingen op ECMO gebied en met name voor mijn aktiviteiten daarin ben ik jullie zeer erkentelijk. Jullie pleidooi voor en aandrang op de realisatie van mijn promotie vanuit het ECMO project hebben verplichtingen opgeroepen, waaraan ik heden, ik hoop naar wens, heb kunnen voldoen.

Stafleden, fellows, AGNIO`s , AGIO`s en verpleegkundigen van de afdeling neonatologie (huidig werkplek management Prof. Dr M. v.d. Bor en Mw. T Vanlier), ik ben jullie veel dank verschuldigd voor alle hulp, die jullie mij veelal onbewust verleend hebben. Jullie voerden de dagelijkse ECMO behandelingen uit en hielden de registratie van de ECMO-run nauwkeurig bij Jullie notities en handelingen zijn de basisgegevens geweest, die ik heb kunnen bewerken voor dit proefschrift

Mw H Wilbers, beste Henriette, jij hebt je als een ware ECMO-coordinatrice gemanifesteerd. Je bent een belangrijke schakel bij de aanschaf en onderhoud van de apparatuur, bij de dagelijkse uitvoer van het ECMO program, bij het verzamelen en verwerken van gegevens, bij het signaleren van knelpunten, bij de scholing en bijscholing van verpleegkundigen en bij de vele experimenten Ik hoop dat de prettige samenwerking voortgezet zal worden de komende jaren.

Mijn kinderchirurgische collegae, Drs. R S.V M. Severijnen en Dr. P.N.M.A. Rieu, beste René en beste Paul, reeds vele jaren (respectievelijk 24 en 10 jaren) delen wij onze werkzaamheden, waarbij wij elkaar steeds aanvullen. In nauw groepsverband hebben wij gezamenlijk gestreefd naar een hoog niveau van patientenzorg met een menselijke benadering. Ik heb van jullie altijd veel steun mogen ondervinden zowel bij de dagelijkse klinische werkzaamheden, waaronder ECMO, als ook bij mijn poging vanuit ECMO een proefschrift te realiseren Vooral het laatste halve jaar hebben jullie vele klinische werkzaamheden van mij overgenomen om mij in de gelegenheid te stellen dit werkstuk af te ronden Ik ben jullie daarvoor dankbaar en hoop dat in de toekomst deze samenwerking op dezelfde goede wijze voortgezet kan worden

Alle " ECMO- en CDH- kinderen", om wie al deze studies in dit proefschrift draaien. Jullie hebben samen met jullie ouders en met ons een nieuwe weg ingeslagen, die andere ervaringen opleverden het was lang niet altijd een gemakkelijke weg Er zijn maar weinig mensen, die begrijpen, wat jullie hebben meegemaakt Wij hopen met elkaars steun de ingeslagen weg te kunnen vervolgen, immers· "samen uit, samen thuis".

Medewerkers van het Centrale Dierenlaboratorium (hoofd Dr J. Koopman), de heren Th. Arts, F Philipsen en A Peters, beste Theo, Fred en Ton, met genoegen kijk ik terug op onze eerste ECMO stappen en de voorbereidingstijd van het ECMO program in het CDL. Een stukje nostalgie, een driedaagse ECMO sessie gedurende een lang weekend in het CDL,

gedurende dag en nacht..... met een oude fiets via het onderaardse gangenstelsel bloedgasjes wegbrengen naar het centraal laboratorium (CKCL). Jullie betrokkenheid en vakmanschap bij deze ECMO sessies, maar ook jullie ludieke oplossingen voor zich voordoende problemen zijn zeer gewaardeerd.

Medewerkers van de afdeling Extracorporale Circulatie (hoofd P. Weerwind), beste perfusionisten, ECMO heeft zeker een extra verzwaring van jullie taak betekend, maar ECMO heeft ongetwijfeld ook de grenzen van jullie werk verlegd, jullie kennis verdiept en nieuwe ervaringen opgeleverd. Jullie kennis, inbreng en betrokkenheid zullen ook in de toekomst op prijs gesteld worden.

Drs. J. Collins, beste James, op spontane wijze heb jij aangeboden het manuscript te lezen en te corrigeren. Mochten er toch nog fouten in staan dan treft jou in elk geval geen blaam.

Door vele mensen zijn van tijd tot tijd extra inspanningen geleverd voor ECMO in het algemeen of voor mij in het bijzonder. Ook deze mensen wil ik bedanken, zoals

- Wil Hermans en Theo van Rijswijk van de Instrumentele Dienst Oost (hoofd A Steenveld)
- Doortje, Liset en Petra van het secretariaat Kinderchirurgie
- Corrie van het secretariaat Neonatologie
- Dhr. J. Meeuwissen van de Medische Fotografie
- Medewerkers van het centrale OK-complex en Anaesthesie
- Medewerkers van de Bloedtransfusiedienst, Radiologie en CKCL

En dan het sluitstuk, zoals steeds als al het werk gedaan is, dan is er pas tijd voor het thuisfront. Voor een deel zit dat in het karakter van het werk, voor een deel zit dat in het karakter van mijzelf. Voor jullie, die mij kennen, is het niet zo vreemd, dat ik juist dit werk doe

Lieve Nicole, je hebt tot de dag van vandaag het gehele ECMO traject van dichtbij meegemaakt. vanaf de eertse onzekere stappen op ECMO-gebied, de opzet van het ECMO program tot nu uiteindelijk deze dissertatie. Aanvankelijk was je alleen secretarieel sterk verbonden met ECMO. Dit werd anders, toen ik besloot via ECMO tot een promotie te komen. ECMO kreeg voor ons beiden ook een sterk emotionele betekenis. In vele opzichten heb ik een beroep op je gedaan. Ik veronderstelde niet alleen begrip voor mijn drukke werkzaamheden en daarnaast mijn promotiedrang, maar tevens verwachtte ik een gewillig oor en geduld, wanneer de zaken niet zo liepen, als ik wenste Met name als de werkzaamheden voor deze promotie gedurende weken en soms maanden noodgedwongen stil lagen Bovendien leverde je mij de hoog noodzakelijke secretariele ondersteuning voor de uitwerking van de diverse publicaties en uiteindelijk voor dit proefschrift. Derhalve is deze promotie niet alleen een kroon op mijn werk, maar vooral ook een kroon op jouw werk. Ik hoop, dat een zware last van ons is afgevallen en dat we weer meer tijd voor elkaar zullen krijgen.

Lieve Amber, Max, Barbara en Boukje, jullie hebben je vader vaak moeten missen Naast de drukke dagelijkse werkzaamheden en de – ook voor jullie – met zeer grote regelmaat terugkerende en zwaar belaste bereikbare diensten had die man het ook nog eens in zijn hoofd gezet carrière te maken en te promoveren Als hij dan thuis was, trok hij zich weer terug achter zijn werktafel op zolder, of was hij met zijn hoofd bij heel andere dingen Na vier mislukte pogingen tot een proefschrift ben ik er nu toch in geslaagd te promoveren. Ik hoop, dat ik nu meer rust zal hebben en meer tijd en aandacht aan jullie zal kunnen besteden.
Deze dag is niet zo zeer een afsluiting, als wel een nieuw begin.
Tenslotte vader, ik ben blij, dat je hier vandaag bent. Je hebt samen met "ons " moeder de basis gelegd. Het is jammer, dat moeder dit niet meer mee heeft kunnen maken

Curriculum Vitae

Franciscus H.J.M. van der Staak werd op 17 september 1946 geboren te Vught. In 1964 behaalde hij het eindexamen gymnasium β (beta) aan het St. Janslyceum te 's Hertogenbosch. In 1972 legde hij het artsexamen af aan de Katholieke Universiteit te Nijmegen.
In 1972 en 1973 vervulde hij de militaire dienstplicht: eerst als keuringsarts bij het luchmacht selectie orgaan (LUSO) te Rijen later als basisarts op de Vliegbasis Deelen.
In augustus 1973 startte hij de opleiding Algemene Heelkunde aan het St Radboud Academisch Ziekenhuis te Nijmegen onder leiding van Prof. Dr. W.J.H. Schmidt. De opleiding werd voltooid onder leiding van Prof. Dr. H.H.M. de Boer.
In het kader van de opleiding tot kinderchirurg en voor nadere specialisatie in de kinderoncologie liep hij van januari 1981 tot juli 1981 stage in 3 centra in de Verenigde Staten: Childrens Hospital of Philadelphia (Prof. Dr. C.E. Koop, Prof. Dr. G.J. D'Angio, Prof. Dr. A.E. Evans), Memorial Sloan Kettering (New York, Prof. Dr. Ph. Exelby) and children's Hospital of Los Angeles (Prof. Dr. M.W.M. Woolley).
Sinds 1 augustus 1979 is hij als staflid werkzaam op de afdeling Kinderchirurgie van het Academisch Ziekenhuis Nijmegen St Radboud. (Hoofd: Prof. Dr. C. Festen).
In 1988 werkte hij mee aan het opzetten van het ECMO project. In 1989 volgde hij een ECMO stage in Pittsburgh (PA). In 1990 slaagde de ECMO projectgroep (o.l.v. Prof. Dr. C. Festen) erin ECMO als project voor ontwikkelingsgeneeskundig onderzoek naar Nijmegen te halen. De auteur behoorde tot één van de hoofdonderzoekers van dit ontwikkelingsgeneeskundig onderzoek van de Gezondheidsraad. Vanuit dit project bewerkte hij de gegevens die betrekking hadden op patientjes met congenitale hernia diaphragmatica, van waaruit dit proefschrift tot stand kwam.

Stellingen

behorend bij het proefschrift

Congenital Diaphragmatic Hernia

and

Extracorporeal Membrane Oxygenation

F.H.J.M. van der Staak

1 De overlevingskansen voor kinderen, die geboren worden met een middenrifdefect, zijn verbeterd door de invoering van extracorporele membraanoxygenatie

dit proefschrift

2 Het blijft moeilijk de ernst van een aandoening als congenitale hernia diaphragmatica te kwantificeren

dit proefschrift

3 Antifibrinolytische therapie kan bloedingscomplicaties, die kunnen optreden bij de operatieve behandeling van een middenrifdefect tijdens extracorporele membraanoxygenatie, voorkomen

dit proefschrift

4 Meer morbiditeit is de prijs voor verminderde sterfte onder kinderen met een congenitale hernia diaphragmatica ten gevolge van behandeling met extracorporele membraanoxygenatie

dit proefschrift

5 Het succes van de behandeling met extracorporele membraanoxygenatie kan voor een deel toegeschreven worden aan de sterk geprotocolleerde opzet van de behandeling

6 Bij een onbehandelbare obstipatie, een paradoxe diarree, een acute urineretentie of een eenzijdige bilvergroting is ook bij een kind een rectaal onderzoek absoluut geïndiceerd

Staak Fvd, Festen C Het sacrococcygeale teratoom een wondergezwel of een monstergezwel? Ned Tijdschr Geneeskd 128 1745 1748, 1984

7 Zolang er geen fysisch-diagnostisch criterium bestaat, op grond waarvan een niet goed ingedaalde testis met voldoende zekerheid onderscheiden kan worden van een retractiele testis, blijft het zogenaamde ballenkaartje een bittere noodzaak

8 Een pasgeborene, die gallig spuugt, behoeft een kinderchirurg.

9 Het zonder meer samenbrengen van verschillende specialisten betekent op zich nog geen teamverband.

Festen C. Geneeskunde in groepsverband. Openbare les 1976

10 De worsteling tussen symbiose en autonomie is een permanent conflict, dat ieder mens met zich meedraagt. De stand in deze strijd is bepalend voor de kwaliteit van samenwerken, samenwonen en samenleven.

11 De Nederlandse Vereniging voor Kinderchirurgie, geboren in 1981 en opgegroeid onder de vleugels van de moedervereniging (de Nederlandse Vereniging voor Heelkunde) heeft de puberteit bijna doorlopen. Het resultaat van de opvoeding, t.w. een evenwichtige en volwassen relatie tussen beide verenigingen, gloort reeds.

vrij naar :
Hazebroek FWJ. Kinderchirurgie, gisteren en morgen Ned Tijdschr Heelk 6: 78-79,1997

12 Bereikbare diensten zijn een bron van spanningen en conflicten. Het verwachtingspatroon dat betrokken partijen van deze dienst hebben, is onvoldoende op elkaar afgestemd, terwijl de aard, de frequentie en de waardering van de dienst onvoldoende zijn geregeld.

13 Het verwerken van een groot databestand met een trage computer is als het eten van soep met een vork.

14 Het gevoel van de recreatie-fietser en van de woon-werk-fietser, dat de wind zeer vaak tegen zit (zowel op de heen- als op de terugweg), kan wetenschappelijk via de wetten van de mechanica ondersteund worden.

15 Het Oudhollandse gezegde "de eerste klap is een daalder waard" is achterhaald door het huidige professionele toptennis.